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Attestation

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

00120896.6

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INFLUENZA VACCINE AND METHOD OF MANUFACTURE

TECHNICAL FIELD

5 The present invention is in the field of virology and vaccine development and relates to novel influenza vaccines based on attenuated, particularly cold adapted and temperature sensitive, influenza A and B strains.

The invention further relates to a simple and efficient process for isolating
10 viruses from various sources and for producing live attenuated influenza vaccines in a serum-free Vero cell culture under conditions where alterations in the surface antigens of the virus due to adaptive selection are minimized or prevented, and to vaccines derived therefrom.

15 BACKGROUND OF THE INVENTION

The influenza hemagglutinin (HA) antigen is the major target for the protective immune responses of a host to the virus.

A common practice of recovering new viral isolates involves recovery from a
20 nasal or throat swab or from a similar source, followed by cultivation of the isolates in embryonated chicken eggs. The virus adapts to its egg host and large scale production of the virus can be carried out in eggs. Such conventional methodology involving embryonated chicken eggs to produce influenza vaccine is, however, extremely cumbersome, involving the handling of many thousands
25 of eggs per week as well as extensive purification of the virus suspension derived from the allantoic fluid to ensure freedom from egg protein.

Another disadvantage in the use of chicken embryos for virus production lies in the fact that this substrate strongly favors the selection of virus variants that
30 differ in their antigenic specificity from the wildtype virus and not rarely results in viruses that may not be suitable for vaccine production due to their altered phenotypes including, for instance, considerable reduction in immunogenicity.

Many attempts have therefore been undertaken in the art to utilize standard
35 tissue culture technology with established mammalian cell lines, such as MDCK (Madin-Darby Canine Kidney) or Vero (African Green Monkey Kidney) cells, for virus production, particularly influenza virus production.

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One of the difficulties in growing influenza strains in tissue cell culture arises from the necessity for proteolytic cleavage of the influenza hemagglutinin in the host cell. Cleavage of the virus HA precursor into the HA1 and HA2

5 subfragments, although not necessary for the assembly of the viral elements to form a complete virion, is required, however, to render the virion infective, i.e. to enable it to infect a new cell.

It has been reported (e.g. Lazarowitz et al., "Enhancement of the Infectivity of
10 Influenza and B Viruses by Proteolytic Cleavage of the Hemagglutinin
Polypeptide", Virology, 68:440-454, 1975) that the limited replication of several
Influenza A strains in standard cell cultures could be overcome by the addition
of proteases like trypsin to the tissue culture medium. Yet, there remained
difficulties in some cases, for instance when using Vero cells.

15 Kaverian and Webster (J Virol 69(4):2700-2703, 1995) report that in Vero cell
cultures, and less pronounced in MDCK, swine kidney, or rhesus monkey kidney
cell cultures, the trypsin activity in the medium rapidly decreased from the onset
of incubation resulting in the failure of virus accumulation in the medium due to
20 the lack of production of a sufficient number of infective virions. They
concluded that a trypsin inhibiting factor was released from the Vero cells. They
further showed that by repeated addition of trypsin reproduction of virus could
be resumed and maintained for a number of reproduction cycles resulting in a
much better virus yield.

25 Another way for efficient vaccine production was reported in US 5,753,489
wherein serum-free medium was used for virus propagation in a number of
different mammalian cells including MDCK and Vero cells. The method disclosed
therein comprises growing vertebrate cells in serum-free medium, infecting the
30 cell culture with a virus, incubating the cell culture infected with the virus,
removing a portion of the virus-containing medium and contacting this portion
with a protease, thereafter adding to that portion a protease inhibitor and
returning that portion to the cell culture. It is preferred therein to provide the
steps of growing, infecting and incubating in a first vessel and the steps of
35 trypsin-contacting and inhibitor-adding are performed in a second vessel
connected with the first vessel in a loop so that the steps o can be performed in

a closed cycle. This system allows to use trypsin or other proteolytic enzymes at much higher concentrations than those normally tolerated by cells in culture.

Experiments leading to the present invention have shown, however, that even between mammalian cells such as MDCK and Vero cells, there exist differences with regard to antigenic variations of the virions produced on such host cell systems.

SUMMARY OF THE INVENTION

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It is therefore an object of the present invention to provide for a method for the production of viruses, particularly Influenza viruses, that yields viral progeny that selectively agglutinates human erythrocytes but not chicken erythrocytes, and that preferably has antigenic properties identical with those of the initially inoculated virus strain, e.g. the primary clinical wildtype isolate.

In a preferred embodiment, the nucleic acid sequence of the HA gene and optionally of the NA gene of the propagated virus is identical with the one of the initially inoculated strain (e.g. an epidemic strain, primary clinical isolate of 20 an infected patient).

It is another object of the invention to provide a method for efficient production of a live attenuated vaccine in a single step procedure that does not require any purification steps of the virus suspension harvested from the cell culture 25 supernatant by centrifugation.

It is yet another object of the invention to provide attenuated, cold adapted and temperature sensitive Influenza A and B strains and vaccines made thereof.

30 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graphic illustration of the time course of trypsin inactivation in the supernatant of a Vero cell culture.

35 Fig. 2 is a graphic illustration of the time course of trypsin inactivation in the supernatant of a MDCK cell culture.

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DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the host system is decisive for the antigenic properties of viruses propagated therein. Comparative experiments using embronated eggs,

5 MDCK and Vero cells clearly proved that the initially inoculated virus is likely to undergo antigenic alteration during growth on any one of these substrates

Evidence has accumulated, however, that the alterations are least or even absent for influenza virus strains grown on Vero cells in serum-free medium.

10 Moreover, it turned out that influenza A viruses, at least strains of the H3N2 subtype, exhibit a selectivity for agglutination of human erythrocytes but not for chicken erythrocytes. Also, they did not grow on eggs. This was a first indication that these Vero-grown viruses might be more identical with the wildtype virus of the corresponding clinical isolate than the ones grown on
15 MDCK cells or eggs.

Indeed, comparison of the HA and NA gene sequences of wildtype isolates obtained from nasal swabs with the ones of the same viruses after growth on Vero and MDCK cells, respectively, revealed alterations in the HA or NA of
20 MDCK-grown viruses relative to the swab isolates or Vero-grown viruses or both.

Moreover, experimental data obtained from immunizations of ferrets with Vero- and MDCK-grown wildtype viruses indicate a far stronger virulence of the Vero-
25 grown viruses compared to the MDCK-grown viruses. Also, the immunogenicity of the Vero-grown viruses tested in an animal trial on macaques was demonstrated to be significantly superior to the one of the MDCK- or egg-grown viruses.

30 These findings together provide strong evidence for the hypothesis that the process for the multiplication and propagation of viruses according to the present invention as hereinafter described in more detail yields viruses that are either unaltered compared to the initially inoculated (e.g. wildtype) virus or are modified to only a minor extent that was not known or achieved in the art
35 hitherto.

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It is not only the avoidance of antigenic alterations that makes the present process of virus multiplication so unique, but it is also its striking simplicity which makes it extremely suitable for large scale industrial vaccine production.

It is therefore an object of the present invention to provide a process for the manufacture of an influenza vaccine that is simple, highly efficient and yields a safe, attenuated live vaccine.

Further experiments have shown that the source of trypsin (or trypsinogen) may be one additional factor that influences the overall yield of infective virions.

- 10 Indeed, while the methods known in the art (e.g., Kaverin and Webster, J Virol 69/4:2700-2703, 1995; or US 5,753,489) use either repeated addition of trypsin (Kaverin and Webster) or high trypsin concentrations (US 5,753,489), the process according to the present invention applies only half or less of the trypsin concentrations reported in the prior art. Moreover, a single addition of as little as 0.5 - 10 µg, preferably 2 - 5 µg trypsin per ml to the cell culture medium is sufficient to reach optimal infective virus titers. Inactivation experiments revealed that porcine or human recombinant trypsins are far less susceptible to inactivation by Vero or MDCK cells than bovine trypsin. Since bovine trypsin is most commonly used in the art it is rather likely that prior art literature unless explicitly mentioning another trypsin source, implicitly refers to bovine trypsin only. This would also help to explain the modes and concentrations of trypsin application recited, for instance, in Kaverin et al. and in US 5,753,489.
- 20
- 25 Using porcine or human rec trypsin for supplementing the serum-free medium for Vero cell cultures according to the present invention therefore allows to use extremely low trypsin concentrations and thus prevent the need of labor-intensive and costly purification steps after harvesting of the virus-containing supernatant.
- 30 Another step that contributes to make the present process simple and therefore attractive to vaccine manufacturers is the addition of a single dose of highly active endonuclease to the cell culture medium at the beginning of incubation of the infected Vero cells for virus propagation. This endonuclease, preferably Benzonase™, is added once to the medium at a very low concentration of 2 - 30, preferably 5 - 15, Units per ml of medium and effectively clears the cell culture medium from free DNA and RNA originating mainly from the lysing or

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lysed host cells. The residual Benzonase enzyme concentration in the ready-for-use vaccine preparations obtained from the centrifuged supernatant remains at 5 ng or less per dose.

5 BenzonaseTM is a trademark of Nycomed Pharma A/S Denmark and relates to an extracellular unspecific endonuclease obtained from *Serratia marcescens*. Benzonase is a genetically engineered endonuclease which degrades both DNA and RNA strands in many forms to small oligonucleotides. It promotes quick reduction of the viscosity of cell lysates, which facilitates ultracentrifugation. It
10 reduces proteolysis and increases the yield in targeted protein and offers complete elimination of nucleic acids from, e.g. recombinant, proteins. It has an exceptionally high activity of 400,000 U/mg.

A third and important advantage of the present process is the factor time hence
15 process costs. Due to the use of serum-free medium that does not contain proteins of animal origin nor antibiotics, expensive and time-consuming purification procedures can be reduced to a minimum or even totally avoided. Also, as the addition of exogenous enzymes such as the protease (e.g. trypsin or trypsinogen) and nuclease (e.g. Benzonase) occurs once at the beginning of
20 the virus propagation phase this saves plenty of time that the state-of-the-art methods require for post-incubation treatment of the virus-containing culture supernatant (e.g., HA activation, RNA/DNA digestion, protein purification, etc.). Surprisingly, it turned out that the early addition of either or both of trypsin and Benzonase to the virus-infected Vero-cell culture had no negative implications
25 on the virus yield, which is probably due to the very low enzyme concentrations applicable in the process of the present invention.

The present process of virus propagation is particularly useful for the multiplication of influenza A viruses of the H3N2 subtype, but is of course also
30 suitable for the isolation and reproduction of any epidemic or laboratory influenza virus strain, regardless of the kind of virus inoculum (e.g., blood serum sample, nasal wash, nasal swab, pharyngeal swab, saliva, etc.). Using the principles of this process, a number of influenza A and B vaccines has been produced which are part of the present invention and which are characterized
35 in more detail in the subsequent Examples. Also, protective efficacy as well as vaccine safety have been confirmed for the vaccines made according to the present invention, as will be demonstrated in the Examples.

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In order that the Invention described herein may be more fully understood, the following Examples are set forth. They are for illustrative purposes only and are not to be construed as limiting this invention in any respect.

5 Example 1: Virus production

Cultivation of Vero /SF (=serum-free) cells:

SF-Medium: DMEM (Biochrom F0435), Ham's F12 (Biochrom F0815), 5mM L-

10 Gln, 0.1% SF-supplement (a) or (b); antibiotics (only for first passage of virus isolation).

SF-Supplement: protein hydrolysate of non-animal origin, without functional proteins such as insulin, transferrin or growth factors:

a) 62.5 g hy-soy/UF, Quest 5X59100, to 500 g HQ-water, filtered with PES 0.2 µm filter;

15 b) 12.5 g hy-pep 1510, Quest, to 100 g HQ-water, filtered with PES 0.2 µm filter.

The content of a deep frozen (liquid nitrogen) disinfected (70% ethanol) ampule

20 of WCB Vero cells was thawed and added to 9 ml of cold serum-free (SF) medium in a 10 ml tube and centrifuged for 10 min at 1000rpm (170 g). The pellet was resuspended in SF-medium to a total of 30 ml, transferred to a 80 cm² Roux bottle and incubated at 37°C and 7%CO₂ for at least 15 min.

Thereafter, the medium was removed and the cells were washed with approx.

25 0.1 ml/cm² PBS def.(= PBS without Ca²⁺ and Mg²⁺). Addition of trypsin/EDTA-solution (8-10 µl/cm²; 0.1% trypsin / 0.02% EDTA-solution) and incubation at room temperature for about 3 min. Detaching by gently pushing the Roux bottle against palm of the hand, addition of SF-medium and trypsin inhibitor (Sigma, T6522) at a quantity of about 1/5 of volume of the

30 trypsin/EDTA solution. Repartition of the cell suspension to Roux bottles or roller bottles, incubation at 37°C and 9% CO₂.

MDCK cells were grown in DMEM/Ham's F12 + 2% FCS (heat inactivated); embryonated hen eggs were 11-12 days old and of SPF (specific pathogen free)

35 origin.

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Propagation of virus strains:

Old medium from roller bottles containing Vero cells was removed and cells were infected with virus by addition of 5 ml virus suspension in SF-medium to 5 each roller bottle, resulting in an MOI (multiplicity of infection) of approximately 0.01. After incubation for 45 minutes at 33°C the virus inoculum was removed with a pipette. 90ml of SF-medium supplemented with 0.5 - 10, preferably 2 - 5 and most preferably 2 µg/ml porcine trypsin (supplier: AvP) or human recombinant trypsin or trypsinogen (own production) and 0.5 g/l sodium bicarbonate were added to each roller bottle and the bottles incubated at 33°C and 5% CO₂. For the production of attenuated live vaccine samples for use in animal testing and in human clinical trials the SF-medium was supplemented with trypsin and, additionally, with Benzonase™ at a concentration of 2 - 30, preferably 5 - 15, and most preferably 10 Units of Benzonase™ per ml of 10 medium. Virus was harvested after 64 hours post infection by centrifugation of the culture supernatant for 5 min at 4000 rpm (3000g) at 10°C in 50 ml-tubes. The supernatant was pooled for each virus strain and stored at +4°C. Aliquots thereof were used for vaccine testing.

15 20 For storage purposes the virus preparations may be freeze-dried and stabilizer such as, for example, trehalose and lactalbumin enzymatic hydrolysate in HEPES buffer may be added. Reconstitution may be done with sterile water.

Example 2: Comparison of trypsin inactivation in cell cultures

25

Table 1: Trypsin inactivation

	0 h	24 h	48 h	72 h
bovine trypsin	0.314	0.189	0.11	0.026
porcine trypsin	0.23	0.201	0.171	0.133
porcine trypsin	0.129	0.108	0.081	0.054
human rec trypsin	0.097	0.054	0.026	0.008

Supernatants obtained from uninfected Vero cell cultures (grown in SF medium as described in Example 1) and MDCK cell cultures (grown in FCS-supplemented 30 medium as described in Example 1) were tested for their capacity to inactivate trypsin of different origin that has been added to the supernatant at time = 0 h at equal concentrations each. Porcine trypsin has been applied in two different

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qualities (obtained from different manufacturers). The results are presented in Table 1 and in Figures 1 and 2.

The data unambiguously show that bovine trypsin is rapidly inactivated in Vero cell culture supernatant and less rapidly in MDCK cell culture supernatant. Porcine and human rec trypsin (manufactured in our laboratories) remain fully active in MDCK supernatants while they are gradually inactivated in Vero supernatants at approximately half or less of the velocity of bovine trypsin inactivation. The difference of the procine trypsins tested is only in the starting 10 OD-level at 247 nm, while the inactivation characteristics are essentially identical for both lots of porcine trypsin.

Example 3: Comparison of various viral properties after growth on different host cell substrates

15

Virus propagation was carried out as described in Example 1 for the different host cell substrates.

Table 2: Characteristics of H3N2 viruses isolated from clinical material on
20 Vero/SF cells

Isolate number	Antigenically related to	Isolated on	HA titer with		Growth in eggs
			chicken erys	human erys	
A/47/96	A/Johannesburg/33/94	Vero	-	+	-
		MDCK	+	+	+
A/7729/98	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+
A/1143/99	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+
A/1144/99	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+
A/1178/99	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+
A/1180/99	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+
A/1182/99	A/Sydney/5/97	Vero	-	+	-
		MDCK	+	+	+

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Each of the seven isolates recovered on Vero cells was reactive with human erythrocytes but not with chicken erythrocytes and none of them accumulated in embryonated eggs. On the other hand, all isolates recovered on MDCK cells were reactive both with chicken and human erythrocytes and were capable of growing in eggs. Although these differences were not seen in influenza A viruses of the H1N1 subtype nor in influenza B isolates (see subsequent Tables 3 and 4), it may nevertheless be assumed that cultivation of influenza viruses on Vero cells will maintain antigenic properties more properly than cultivation on other substrates.

5

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Table 3: Characteristics of H1N1 viruses isolated from clinical material on Vero/SF cells.

Isolate number	Antigenically related to	Isolated on	HA titer with		Growth in eggs	Changes in HA1 at position
			chicken erys	human erys		
A/5389/95	A/Bayern/7/95	Vero	+	+	+	D
		MDCK	+	+	+	D
A/1035/98	A/Beijing/262/95	Vero	+	+	+	D
		MDCK	+	+	+	D
		Egg	+	+	+	G
		Swab				D
A/1131/98	A/Beijing/262/95	Vero	+	+	+	D
		MDCK	+	+	+	D
		Swab				D
A/1134/98	A/Beijing/262/95	Vero	+	+	+	D
		MDCK	+	+	+	D
		Egg	+	+	+	n.t.
		Swab				D

From the data in Table 3 it appears that H1N1 influenza viruses may be less susceptible to adaptive selection, as the Vero and MDCK-grown isolates do not exhibit significant differences in their hemagglutination characteristics nor in their HA sequences. A similar conclusion may be drawn for the B isolates listed in Table 4.

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Tabelle 4: Characteristics of B viruses isolated from clinical material on Vero/SF cells

Isolate number	Antigenically related to	Isolated on	HA titer with		Growth in eggs	Changes in HA1 at position
			chicken erys	human erys		
B/4291/97	B/Beijing/184/93	Vero	+	+	+	identical
		MDCK	+	+	+	
B/1/99	B/Beijing/184/93	Vero	+	+	+	T(g.s)
		MDCK	+	+	+	T(g.s)
		EGG	+	+	+	A
		Swab				T(g.s)
B/110/99	n.t.	Vero	+	+	+	identical
		MDCK	+	+	+	
B/147/99	n.t.	Vero	+	+	+	identical
		MDCK	+	+	+	
B/166/99	B/Beijing/184/93	Vero	+	+	+	identical
		MDCK	+	+	+	
B/167/99	B/Beijing/184/93	Vero	+	+	+	identical
		MDCK	+	+	+	

The clinical starting material (e.g. serum samples, swabs) for virus isolation and replication was primarily obtained from:

1. Institute of Virology, Vienna, Austria (Prof. F. Heinz) 1995/96, 1996/97
2. Unité de Génétique Moléculaire des Virus Respiratoires, Institut Pasteur, Paris, France (Prof. S. van der Werf) 1996/97
3. Public Health Laboratory Service, London, UK (Dr. M. Zambon) 1996/97
4. Laboratoire Central de Virologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland (Dr. W. Wunderli) 1996/97, 1997/98
5. Virus Unit, Queen Mary Hospital, Hong Kong (Dr. W.L. Lim) 1997/98

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Table 5: Amino acid changes in HA, NA and M proteins of H3N2 influenza viruses isolated on different host systems

Isolate number	Changes at positions								
	HA						NA		M
	128	129	229	133	218	220	136	151	
A/47/96 Vero	T(g.s)								
A/47/96 MDCK	A								
A/7729/98 Vero		E	R						
A/7729/98 MDCK		G	K						
A/1143/99 Swab				N(g.s)	G		n.t	n.t	
A/1143/99 Vero				N(g.s)	G			D	n.t
A/1143/99 MDCK				D	E			G	Identical
A/1144/99 Swab						R	n.t		n.t
A/1144/99 Vero						R	identical		identical
A/1144/99 MDCK						G			
A/1179/99 Swab	Identical						n.t		n.t
A/1179/99 Vero							identical		identical
A/1179/99 MDCK									
A/1180/99 Swab	identical					n.t	n.t		n.t
A/1180/99 Vero						Q			identical
A/1180/99 MDCK						R			
A/1182/99 Swab	Identical					n.t		n.t	
A/1182/99 Vero						n.t		n.t	
A/1182/99 MDCK						n.t		n.t	

The results show that with some isolates there was no alteration of the HA sequence of Vero or MDCK propagated viruses over the HA sequence directly obtained from the swab material by PCR amplification. In some other isolates grown on MDCK cells the HA and/or NA sequences were deviating from the corresponding sequences obtained on Vero cells. The Vero-derived viruses did not show, however, any deviations in the HA sequence over the HA sequence of the swab isolates, where determined.

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Table 6: Immunogenicity of Vero-, MDCK- and Egg-derived viruses for macaques

Animal number	Virus for immunization	Dose, PFU/ml	Serum HI titers
96	A/Vienna/47/96 V	5x10 ⁴	256
88	A/Vienna/47/96 V	5x10 ⁴	128
15	A/Vienna/47/96 V	1.0x10 ⁶	128
95	A/Vienna/47/96 V	1.0x10 ⁶	256
93	A/Vienna/47/96 M	1.0x10 ⁶	16
128	A/Johannesburg/33/94 E	5x10 ⁸	32
110	A/Vienna/157/97 V	5x10 ⁴	128
78	A/Wuhan/359/95 E	5x10 ⁸	32

The Macaques were immunized i.n. in the absence of anesthesia with 1 ml of virus suspension

5. V - Vero- isolated virus

M - MDCK -isolated viruses

E - egg isolated viruses

10 Table 7: Virulence of Vero- and MDCK- derived variants of A/Vienna/47/96 wt virus for ferrets

Viruses	Virus dose, PFU/ml	Number of animals with fever on day		
		1	2	3
A/Vienna/47/96 Vero	2x10 ²	F	FFF	
	1x10 ³	FFF	FFF	
A/Vienna/47/96 MDCK	5x10 ²			
	5x10 ³		FF	
	5x10 ⁴	FF	F	F

Animals were immunized i.n. under ether narcosis with 1 ml of virus suspension.

N- normal temperature from 38.1°C to 39.9°C;

F- fever, more than 40.0°C.

15 The most surprising, yet important result in Table 6 is the very low immunogenicity of MDCK-derived A/Vienna/47/96 virus compared with the corresponding Vero-derived virus. It is no particular surprise that the egg-derived viruses show only poor immunogenicity.

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Similarly, the results listed in Table 7 indicate that Vero-derived viruses are less if at all altered by adaptive selection on their host substrate than the MDCK-derived viruses. This means that the Vero-derived viruses maintain more or even all of the immunologically relevant, particularly antigenic, properties of the 5 original virus than is the case with the MDCK-derived viruses.

Example 4: Vaccine production with preferred strains

The process described in Example 1 was also used for the production of vaccine 10 samples for animal testing and human clinical studies. It is understood that the process of virus propagation described therein also encompasses variations that could be suggested or applied by a person of ordinary skills in the art without inventive input and as long as the variations do not change the sense of the present invention as described herein and in the claims.

15 Vaccine samples containing one or more of the preferred influenza A or B wildtype strains, master strains or reassortant strains (that are subsequently described in more detail) were exclusively produced using the continuous Vero cell line as the host cell system (unless for purposes of comparison with 20 samples obtained from other host substrates) in serum-free medium additionally supplemented with the nutritional ingredients and enzymes as described in Example 1.

25 The methods used to modify the wildtype viruses to arrive at the preferred influenza master strain candidates of the present invention including the methods of attenuation (e.g., temperature sensitivity), cold adaptation and reassortment are known in the art and extensively reviewed, for instance, in WO 99/64068.

30 Further characteristics of the two most preferred influenza A and B master strain candidates useful for attenuated live vaccine production, e.g., by 6/2 reassortment with the HA and NA genes of actual epidemic influenza viruses recommended by the WHO, are given in the following Tables 8 - 13.

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Table 8: Characteristics of master strain candidates for live influenza vaccines

	Influenza A A/Singapore/1/57/ca H2N2	Influenza B B/Vienna/1/99/ca
Passage history	A/Singapore/1/57 wt egg derived H2N2 20 passages at 37°C on Vero/SF cells 25 passages at 25°C on Vero/SF cells	B/Vienna/1/99 wt Vero derived 1 additional passage at 33°C on Vero/SF cells 22 passages at 25°C on Vero/SF cells
Method of attenuation	Serial passages at optimal and suboptimal temperature on heterologous system	Serial passages at optimal and suboptimal temperature on heterologous system
Phenotypic markers	temperature sensitive (ts) cold adapted (ca) very low reproduction in mouse lungs	temperature sensitive (ts) cold adapted (ca) very low reproduction in mouse lungs
Genotypic markers	Mutations: 13 (8 coding) PB2 3 (2 coding) PB1 2 (1 coding) PA 4 (3 coding) NP 1 M 2 (2 coding) NS 1	Mutations: 5 (3 coding) PB2 0 PB1 1 PA 0 NP 2 (1 coding) M 1 NS 1

Table 9: Full Sequence of the 8 genome segments and of the 10 corresponding proteins of strain A/Singapore/1/57/ca

A/Singapore/1/57/ca (H2N2)			
RNA segment	Nucleotide sequence (cDNA)	Protein	Amino acid sequence
1	SEQ ID No. 1	PB2	SEQ ID No. 9
2	SEQ ID No. 2	PB1	SEQ ID No. 10
3	SEQ ID No. 3	PA	SEQ ID No. 11
4	SEQ ID No. 4	HA	SEQ ID No. 12
5	SEQ ID No. 5	NP	SEQ ID No. 13
6	SEQ ID No. 6	NA	SEQ ID No. 14
7	SEQ ID No. 7	M1	SEQ ID No. 15
		M2	SEQ ID No. 16
8	SEQ ID No. 8	NS1	SEQ ID No. 17
		NS2	SEQ ID No. 18

Exhibit 12-200

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ca - cold adapted

It shall be noted, however, that the genome segments No. 4 and 6, i.e., the HA and NA genes, are not required to characterize the Influenza A master strain 5 candidates, because these genes will be exchanged for the corresponding genes of actual epidemic influenza viruses (as mentioned hereinbefore). The features important for the safety of a vaccine, e.g. temperature sensitivity, or features that allow intranasal (where average temperature is lower than usual body temperature) administration of a vaccine, namely cold adaptation, are primarily 10 caused by mutations in the remaining 6 genome segments.

The following Table 10 lists the mutations in the genome segments of A/Singapore/1/57/ca compared to the corresponding wildtype strain A/Singapore/1/57/wt

15

Table 10: Mutations in the genome segments of attenuated, temperature sensitive, cold adapted Influenza

strain A/Singapore/1/57/ca compared to A/Singapore/1/57/wt strain

RNA segment	Length (n'ds)	Nucleotides changed		Protein	Length (aa)	Amino acids changed		
		position	wt ca			position	wt ca	
1	2341	252	a g	PB2	771	-	-	-
		581*	t c			185	I	T
		1046*	g t			340	R	I
2	2341	1279*	t a	PB1	757	419	L	I
		1985	a c			-	-	-
3	2233	707*	a t	PA	716	228	I	N
		1425	t a			-	-	-
		1537*	a g			505	V	I
		1819*	g c			598	Q	E
5	1565	210	g a	NP	506	-	-	-
7	1027	327*	g a	M1	282	101	R	K
		499*	g c			158	Q	R
				M2	87	-	-	-
8	890	813	a g	NS1	237	-	-	-
						NS2	121	-

Total number of mutations - 13 (8 coding)

20 * coding mutations

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Preferred variants of A/Sing/1/57/ca comprise the ones listed in the following Table 11, wherein "Δ" means "del" or "delta" and stands for a mutant that contains at least one "deletion" in its NS gene segment.

5 Table 11: Preferred variants of A/Sing/1/57/ca

	A/Sing/1/57/ca	Sing ca/ ΔNS 87	Sing ca/ ΔNSPR8	Sing ca/ NS124PR8
PB2 (Sing ca*)	○ ● ●	○ ● ●	○ ● ●	○ ● ●
PB1 (Sing ca*)	● ○	● ○	● ○	● ○
PA (Sing ca*)	● ○ ● ●	● ○ ● ●	● ○ ● ●	● ○ ● ●
HA	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
NP (Sing ca*)	●	●	●	●
NA	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
M1,2 (Sing ca*)	● ● ○	● ● ○	● ● ○	● ● ○
NS1,2 (Sing ca*)	○	○		
NS1,2 (PR8**)			del NS1	Stop 124 NS1
Phenotypes				
ca	+	+	+	+
ts	+	+	+	+
IFN-induct.	-	- (?)	+	+
IFN-sensit	-	+	+	-

* genome segment originating from A/Singapore/1/57/ca

** genome segment originating from Influenza A/PR8/34

ca - cold adapted; ts - temperature sensitive;

aa - amino acid(s)

10 IFN-induct. - strain causes interferon release in host substrates that are able of IFN production, as well as in animal or human immune systems upon administration.

IFN-sensit. - strain is sensitive towards interferon; replication in IFN producing systems is reduced or stopped.

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Sing ca/ΔNS 87 - strain A/Singapore/1/57/ca containing deletion of 87 amino acids in NS1 gene at aa position 36-123.

Sing ca/ΔNSPR8 - strain A/Singapore/1/57/ca containing the NS gene segment from A/PR8/34 (herein also abbreviated "PR8") which contains a 5 deletion of the entire NS1 gene.

Sing ca/NS124PR8 - strain A/Singapore/1/57/ca containing the NS gene segment from A/PR8/34 which contains a stop codon at aa position 124 of the NS1 gene.

10 The following Tables 12 and 13 refer to preferred Influenza B master strain candidates and to variations and reassortants, respectively, thereof.

Table 12: Full Sequence of the 8 genome segments and of the 11 corresponding proteins of strain B/Vienna/1/99/ca

B/Vienna/1/99/ca			
RNA segment	Nucleotide sequence (cDNA)	Protein	Amino acid sequence
1	SEQ ID No. 19	PB2	SEQ ID No. 27
2	SEQ ID No. 20	PB1	SEQ ID No. 28
3	SEQ ID No. 21	PA	SEQ ID No. 29
4	SEQ ID No. 22	HA ₀	SEQ ID No. 30
5	SEQ ID No. 23	NP	SEQ ID No. 31
6	SEQ ID No. 24	NB	SEQ ID No. 32
		NA	SEQ ID No. 33
7	SEQ ID No. 25	M1	SEQ ID No. 34
		BM2	SEQ ID No. 35
8	SEQ ID No. 26	NS1	SEQ ID No. 36
		NS2	SEQ ID No. 37

15 ca - cold adapted

The original strain B/Vienna/1/99 was isolated on Vero cell culture grown with serum-free medium in February 1999 in Vienna, Austria from a 12 year old female with acute influenza. It was rated as B/Beijing/184/93-like by the Center

20 for Disease Control (CDC), Atlanta, USA. After an additional passage at 33°C the wildtype strain - designated as B/Vienna/1/99 wt - was attenuated by 22 serial passages at 25°C using the same cell culture system. The plaque purification was done at 25°C for the first and at 33°C for the following four

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round. The derived plaque purified clone was amplified and stored at -70°C, designated as B/Vienna/1/99 ca or short BV22. The identity as a B/Beijing/184/93-like virus was confirmed by HI-assay with standard anti-serum from NIBSC.

B

Table 13: Mutations in B/Vienna/1/99/ca (=BV22) compared to B/Vienna/1/99/wt (BVie) 1. passage on Vero/SF

Segment (length in nucleotides)	Nucleotides changed			Protein (length in amino acids)	Amino acids changed		
	Posi- tion	BVie	BV22		Posi- tion	BVie	BV22
1 (2396)	-	-	-	PB2 (770)	-	-	-
2 (2369)	594	T	C	PB1 (752)	-	-	-
3 (2305)	-	-	-	PA (726)	-	-	-
4 (1882)	457 1299 1595	G G G	A T A	HA ₀ (584)	142 422 521	A K G	T N E
5 (1844)	128 330	C T	T C	NP (560)	23	S	F
6 (1557)	- 823 1135	- G T	- A C	NB (100) NA (466)	- 257 361	- R I	- Q T
7 (1180)	- 831	- A	- G	M1 (248) BM2 (109)	- 21	- M	- V
8 (1097)	118	G	A	NS1 (281)	25	A	T
	-	-	-	NS2 (122)	-	-	-

Example 5: Vaccine safety and efficacy

10

The subsequent data confirm temperature sensitivity and vaccine safety for influenza vaccines manufactured according to the present invention, e.g., as described in Example 1.

15 Table 14: Antibody response of mice after one intranasal immunisation without narcosis

Viruses	Number of responders ¹	GMT ³	Protection after challenge ²
PR8/Sing ca -2/6	0/6	<4	5/6
PR8/Sing ca -ΔNS	4/6	6.7	5/6
PR8-wt	5/6	16.0	5/6

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1 - number of animals with positive HI titer > 1:4

2 - number of animals without detectable virus in the lungs

3- Geometric mean titer of antibodies in serum

5 PR8wt - influenza strain A/PR/8/34 wildtype (H1N1), pathogenic for mice
 PR8/Sing ca-2/6 - is the reassortant between attenuated influenza strain
 A/Sing/1/57 ca and PR8 wt, containing 2 genes (HA and NA) from PR8wt
 virus and all other genes from A/Sing/1/57 ca.

PR8/Sing-ΔNS contains HA and NA genes from PR8wt, five genes from
 10 A/Sing/1/57 ca and the NS gene of PR8 origin lacking the NS1 coding
 sequence (NS1 deletion or knockout).

Table 15: Antibody response and protection of mice after intranasal immunisation with different variants of A/Singapore/1/57 virus (under narcosis)

Viruses	Responders ¹		GMT after two immunisations	Protection after challenge ⁴
	1-st immunisation	2-nd immunisation		
A/Sing/1/57/wt va ²	9/9	9/8	103.8	9/9
A/Sing/1/57/ca ³	8/10	10/10	65.7	8/10
A/Sing/1/57/ΔNS 87	1/10	10/10	27.8	8/10

1 - number of animals with positive HI titer > 1:4

2 - va- Vero-adapted

3 - ca - cold-adapted

4 - number of animals without detectable virus in the lungs

20

Table 16: Reproduction of wt, va and ca variants of A/Singapore/1/57 in mouse lungs^a

Viruses	Virus titer in mouse lungs post infection on day, PFU/ml ^b		
	2	4	6
A/Singapore/1/57/wt	1.6x10 ⁶	2.2x10 ⁵	1.4x10 ³
A/Singapore/1/57/wt va	2.5x10 ⁸	2.1x10 ⁸	1.0x10 ²
A/Singapore/1/57/ca	<10	<10	<10

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^a Mice were infected i.n. with 50 μ l of virus fluid with a titer 1.0×10^8 PFU/ml.
^b PFU/ml of 10% tissue suspension, titrated on MDCK cells.

Table 17: Virulence of wt and ca variants of A/Singapore/1/57 virus for ferrets

Viruses	Number of animals with fever post infection on day		
	1	2	3
A/Singapore/1/57 wt	FFF	NNN	NNN
A/Singapore/1/57 ca	NNN	NNN	NNN

5

Rectal temperature of animals was recorded twice a day and characterized as follows:

N - normal temperature from 38.1°C to 39.9°C

F - fever, more than 40.0°C .

10 Each group consisted of 3 animals, which were immunized i.n. under ether narcosis with 1 ml of virus fluid with a titer of 2×10^8 PFU/ml.

Table 18: Reproduction of 2/6 reassortant of A/Hong Kong/1035/98 wt and A/Singapore/1/57/ca in mouse lungs^a

Viruses	Virus titer in mouse lungs on day 2-6 post infection, PFU/ml ^b		
	2	4	6
A/Hong Kong/1035/98 wt H1N1	6.8×10^4	2.0×10^4	< 10
A/Singapore/1/57/ca x A/Hong Kong/1035/98 wt	< 10	< 10	< 10

15

^a Mice were infected i.n. under ether narcosis with 50 μ l of virus fluid.

^b PFU/ml of 10% tissue suspension, titrated on Vero/SF cells, data are given as mean value for 6 mice (the lungs of each animal were treated separately).

The reassortant contains the HA and NA genes from A/Hong Kong/1035/98 wt

20 wildtype and the other 6 genes from A/Singapore/1/57/ca.

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Table 19: Virulence of 8/2 reassortant of A/Vienna/47/98 wt and A/Singapore/1/57/ ca for ferrets

Viruses	Virus subtype	Number of animals with fever on day			
		1	2	3	Rhinitis ^b
<i>Master strain</i>					
A/Singapore/1/57/ ca	H2N2	NNN	NNN	NNN	±
<i>Epidemic virus</i>					
A/Vienna/47/98 wt	H3N2	NNN	FFF	FFF	+++
<i>Reassortant</i>					
A/Singapore/1/57/ca x Vienna/47/ 98 wt	H3N2	NNN	NNN	NNN	±

Animals were immunized i.n. under ether narcosis with 1 ml of virus, 2×10^6 PFU/ml.

5 N- normal temperature from 38.1°C to 39.9°C ;

F- fever, more than 40.0°C .

^b + + + - severe rhinitis

± absence of rhinitis

10 The results presented in Tables 16 to 19 clearly demonstrate the safety of the vaccines containing the attenuated, temperature sensitive master strain or, in case of reassortants, of the vaccines based on the reassorted viruses composed of the "backbone" of the attenuated, temperature sensitive master strain (6 genes) and the HA and NA genes from, e.g., the pathogenic wildtype strain
 15 A/Hong Kong/1035/98 wt.

Table 20: Ts and ca phenotype of B/Vienna/1/99

Virus	PFU/ml on Vero cells at	PFU/ml on MDCK cells at	
		25°C	33°C
B/Vienna/1/99 wt	<300	4×10^6	4×10^5
B/Vienna/1/99 ca (BV22)	1×10^6	2.4×10^6	<20

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Table 21: Genetic stability of the ts phenotype of B/Vienna/1/99 ca

Virus	PFU/ml on MDCK cells at	
	33°C	39°C
B/Vienna/1/99 wt	4x10 ⁶	4x10 ⁶
B/Vienna/1/99 ca (BV22)	2.4x10 ⁶	< 20
B/Vienna/1/99 ca (BV22) after 5 passages at 33°C	8x10 ⁵	< 20

The strain BV22 was passaged five times at high MOI on Vero cells. Then the ts-phenotype was controlled again. The strain remained temperature sensitiv as can be seen in Table 21.

5

Table 22: Virulence of B/Vienna/1/99 ca and wt in mouse lungs

Virus	organ	PFU/ml* at day post infection		
		2	3	4
B/Vienna/1/99 ca (BV22)	lung	< 20	< 20	< 20
	nose	1x10 ²	1x10 ²	20
B/Vienna/1/99 wt	lung	8x10 ⁴	7x10 ³	4.4x10 ³
	nose	3.8x10 ⁴	3.4x10 ⁴	1.4x10 ⁴

* 9 OF1 mice per strain were immunized intranasally under ether narcosis with 10³ PFU. At the indicated days post infection 3 mice per group were sacrificed. Lungs and nasal turbinates were homogenized for a 10% (w/v) suspension in PBS def. A plaque assay of the suspensions was performed.

10

The data show that moderate reproduction of the ca master strain candidate BV22 was possible in the nasal mucosa while the ts property of the virus prevented reproduction in the lungs.

15

Table 23: Ts and ca phenotype of the reassortant influenza B strain

Virus	PFU/ml on MDCK cells at	
	33°C	39°C
B/Vienna/1/99 wt	4x10 ⁶	4x10 ⁶
B/USSR/69 wt	1.6x10 ⁶	4x10 ⁴
B/Vienna/1/99 ca (BV22)	1.4x10 ⁶	< 20
BV22 x B/USSR/69 (6/2)	8x10 ⁵	< 20

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A 6/2 reassortant strain containing HA and NA of the wild type influenza strain B/USSR/69 wt and the other 6 genome segments from B/Vienna/1/99 ca (BV22) was established. The origin of the hemagglutinin was tested by HI-assay, all other genome segments by RT-PCT and restriction analysis using 5 methods known in the art.

Table 24: Virulence of the reassortant influenza B strain in mouse lungs

Virus	organ	PFU/ml* at day post infection		
		2	3	4
B/Vienna/1/99 ca (BV22)	lung	<20	<20	<20
	nose	<20	1x10 ²	40
B/USSR/69 wt	lung	1.8x10 ⁵	4x10 ⁵	2.4x10 ⁴
	nose	1.6x10 ⁵	2x10 ⁵	1.6x10 ⁵
BV22 x B/USSR/69 wt (6/2)	lung	<20	<20	<20
	nose	2.8x10 ³	2x10 ³	4x10 ²

* 9 OF1 mice per strain were immunized intranasally under ether narcosis with 10⁵ PFU. At the indicated days post infection 3 mice per group were 10 sacrificed. Lungs and nasal turbinates were homogenized for a 10% (w/v) suspension in PBS def. A plaque assay of the suspensions was performed.

Example 6: Clinical study

15 The following vaccines (in the form of nasal sprays) were produced according to the present invention (e.g. as described in Example 1) for intranasal delivery.
 Composition per ml (after reconstitution of freeze-dried material):
 (1) Placebo: 2x SF-medium, 40mM HEPES buffer, 8% lactalbumin enzymatic hydrolysate, 4% trehalose;
 20 (2) Vero-Vac H1: A/Beijing/282/95 (H1N1)-like preparation comprising 4.3x10⁷ TCID₅₀ of 6/2 reassortant A/Singapore/1/57/ca with A/Hong Kong/1035/98; 2x culture supernatant, 40mM HEPES buffer, 8% lactalbumin enzymatic hydrolysate, 4% trehalose;
 (3) Vero Vac H3: A/Sidney/5/97 (H3N2)-like preparation comprising 2.1x10⁷ TCID₅₀ of 6/2 reassortant A/Singapore/1/57/ca with A/SW/7729/98; 2x culture supernatant, 40mM HEPES buffer, 8% lactalbumin enzymatic hydrolysate, 4% trehalose;
 25 (4) Vero Vac B: B/Beijing/184/93 - like preparation comprising 3.8x10⁷ TCID₅₀ of 7/1 reassortant B/Vienna/1/99/ca (all genome segments

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except HA) with B/Switzerland/4291/97 (HA genome segment); 2x culture supernatant, 40mM HEPES buffer, 8% lactalbumin enzymatic hydrolysate, 4% trehalose;

(5) Vero Vac Trivalent: mixture of (2), (3), and (4):

5	A/Singapore/1/57/ca x A/Hong Kong/1035/984	4.3×10^7	TCID ₅₀
	A/Singapore/1/57/ca x A/SW/7729/98	2.1×10^7	TCID ₅₀
	B/Vienna/1/99/ca x B/Switzerland/4291/97	3.8×10^7	TCID ₅₀

(6) Russian trivalent vaccine (live influenza vaccine for adults):

10	A/17/Beijing/95/25 (H1N1)	1.1×10^8	EID ₅₀
	A/17/Sidney/97/76 (H3N2)	2.3×10^7	EID ₅₀
	B/60/Petersburg/95/20	1.1×10^7	EID ₅₀

(7) Monovalent Vero vaccine BV22: B/Beijing/184/93 - like preparation comprising 2×10^8 TCID₅₀ of master strain candidate B/Vienna/1/99/ca (=BV22); 2x culture supernatant, 40mM HEPES buffer, 8% lactalbumin enzymatic hydrolysate, 4% trehalose;

The vaccines were administrated to 13 volunteers per each vaccination group. 550 µl of reconstituted vaccine (or placebo, respectively) were given intranasally to each patient on day 0 and for a second time on day 22 ± 1. The results are summarized in Table 25 below.

Safety results: The total number of adverse events (AE) during five days after the first and second vaccination was 14 including 9 mild and 4 moderate AE. Only one volunteer showed severe AE, comprising an increase in body temperature up to 38.8°C within 3 hours after the first vaccination without any local or systemic symptoms. During the next four hours his temperature became normal again. After the first vaccination 7 AE were observed. One of them was local and six were systemic. After the second vaccination 2 local and 5 systemic AE were observed.

No significant difference in terms of safety was revealed between the groups of the study including the one with placebo. No serious AE related to the vaccination were observed except for the one mentioned above. Two of the moderate AE occurred in the H3N2 group (temperature elevation up to 37.6° and acute pharyngitis on day 3 in one volunteer; nasal obstruction, discomfort in the throat on day 22-24 and temperature elevation up to 37.5°C in another volunteer), and one in the H1N1 group (pain in the throat, rhinitis from day 22-26, temperature elevation up to 37 - 37.8°C between days 22-24).

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Table 25: Response of seronegative volunteers to Vero Vac vaccines and to a trivalent Russian cold-adapted egg derived vaccine

No	Vaccine for immunization	Virus dose, TCID ₅₀ /ml or EID ₅₀ /ml	No. of volunteers	% of volunteers with at least 4-fold increase of serum HAI antibody titre to antigens		
				H1N1	H3N2	B
1	Placebo		13		(8)	
2	Vero Vac H1 (H1N1)	4.3x10 ⁷	13	46		
3	Vero Vac H3 (H3N2)	2.1x10 ⁷	13		77	
4	Vero Vac B	3.8x10 ⁷	12			60
5	Vero Vac Trivalent	H1 4.3x10 ⁷ H3 2.1x10 ⁷ B 3.8x10 ⁷	12	33	50	33
6	Russian trivalent vaccine: A/17/Beijing/95/26 H1N1 A/17/Sidney/97/76 H3N2 B/80/Petersburg/95/20	1.1x10 ⁸ 2.3x10 ⁷ 1.1x10 ⁷	13	46	8	38
7	Vero vaccine BV22	2x10 ⁶	13			

The results obtained from the clinical study thus confirm a very good safety of
 5 the vaccines produced according to the present invention and using the
 preferred influenza A and B master strain candidates of the present invention.

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CLAIMS

We claim

1. A process for multiplying viruses in a host cell system wherein alterations in the surface antigens of the starting virus due to adaptive selection on said host cell system are minimized or prevented, the process comprising the steps of:
 - a) Infected African Green Monkey Kidney (Vero) cells that have been grown in and separated from a suitable serum-free medium that does not contain functional proteins such as insulin, transferrin or growth factors, by adding to the cells a quantity of a virus suspension and incubating the cells for a period of time;
 - b) after incubation removing the virus suspension from the cells and adding to the cells a quantity of a suitable serum-free medium that does not contain functional proteins such as insulin, transferrin or growth factors and that has been supplemented with human recombinant or porcine trypsin and/or trypsinogen; and
 - c) incubating the cells for another period of time and harvesting the multiplied viruses by collecting the supernatant obtained from centrifugation of the resulting cell culture.
2. The process according to claim 1, wherein the medium in step (b) has been further supplemented with a nuclease enzyme having DNase and/or RNase activity, preferably with Benzonase.
3. The process according to claim 1 or 2, wherein the medium in step (b) has been supplemented once with trypsin in a concentration of 0.5 - 10, preferably 2 - 5 µg per ml medium.
4. The process according to any one of claims 1 to 3, wherein the period of time for incubation in step (a) ranges from 10 - 120 minutes, preferably from 30 - 60 minutes.
5. The process according to any one of claims 1 to 4, wherein the period of time for incubation in step (c) ranges from 24 - 96 hours, preferably from 48 - 72 hours.

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6. The process according to any one of claims 2 to 5, wherein the medium has been supplemented once with Benzonase in an amount of 2 - 30, preferably 5 - 15, U per ml of medium.
- 5 7. The process according to any one of claims 1 to 6, wherein the virus is an influenza A virus, preferably of subtype H3N2, or influenza B virus.
8. The process according to claim 7, wherein the virus is an attenuated, cold adapted, temperature sensitive influenza virus selected from the group consisting of A/Sing/1/57ca, A/Sing/1/57ca/ΔNS 87, A/Sing/1/57ca/ΔNSPR8, A/Sing/1/57ca/NS124PR8, B/Vienna/1/99 ca, and any attenuated variants and reassortants derived from these strains.
9. An influenza vaccine obtainable in a process as defined in any one of claims 1 to 8, in combination with a suitable carrier.
10. The vaccine according to claim 9, for intranasal delivery.
11. An attenuated, cold adapted, temperature sensitive influenza virus selected from the group consisting of influenza virus strains A/Sing/1/57ca, A/Sing/1/57ca/ΔNS 87, A/Sing/1/57ca/ΔNSPR8, A/Sing/1/57ca/NS124PRB, and B/Vienna/1/99 ca, and any attenuated variants and reassortants derived from these strains.
- 25 12. The influenza virus according to claim 11, obtainable in a process as defined in any one of claims 1 to 8.
13. A vaccine comprising at least one influenza virus defined in claim 12, in combination with a suitable carrier.
- 30 14. The vaccine according to claim 13 for intranasal delivery.
15. The vaccine according to claim 13 or 14, obtainable in a process according to any one of claims 1 to 8.

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ABSTRACT

The invention relates to a simple and efficient process for isolating viruses from various sources and for producing live attenuated influenza vaccines in a serum-

5 free Vero cell culture under conditions where alterations in the surface antigens of the virus due to adaptive selection are minimized or prevented. The process does not require purification of the virus-containing supernatant harvested from the cell culture nor post-incubation treatment of the viruses for HA activation.

10 The invention further relates to influenza A and B master strain candidates and to vaccines made thereof.

Fig.1

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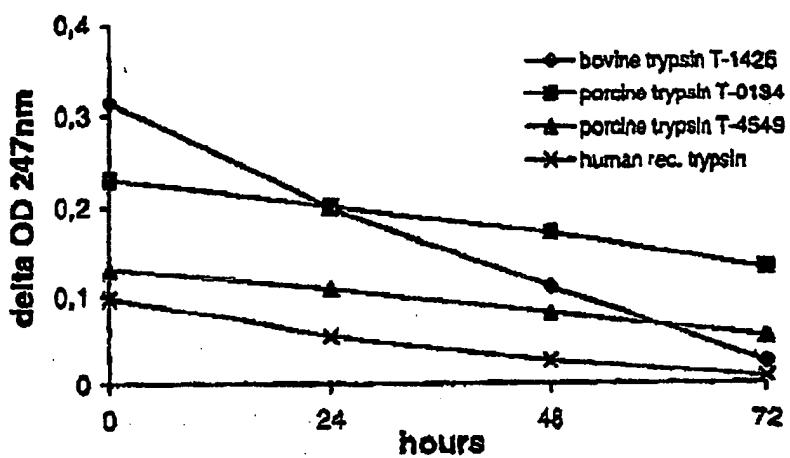


Fig. 1

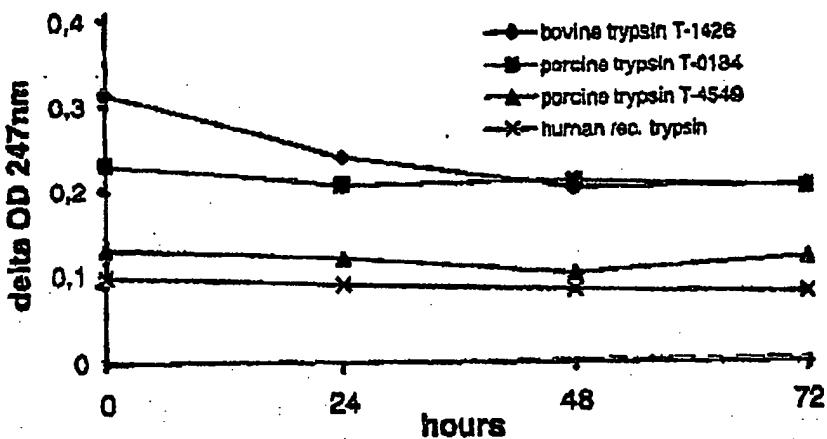


Fig. 2

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SEQUENCE LISTING

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<120> INFLUENZA VACCINE AND METHOD OF MANUFACTURE

<130> BEP-4867-EU (Influenza vaccine)

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<170> PatentIn Ver. 2.1

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SPEC

500-203

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62133 Influenza virus A/Singapore/1/57/ca

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<212> DNA
<213> Influenza virus A/Singapore/1/57/ca

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SPECIMEN

१०७२६

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<213> Influenza virus A/Singapore/1/57/ca

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filed 09-12-2001

SPEC

09-12-2001

<211> 1568

<212> DNA

<213> Influenza virus A/Singapore/1/57/ca

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<211> 1466

<212> DNA

<213> Influenza virus A/Singapore/1/57/ca

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<211> 1027
<212> DNA
<213> Influenza virus A/Singapore/1/57/can

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<213> Influenza virus A/Singapore/1/57/can

<400> 8

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<211> 771

<212> PRT

<213> Influenza virus A/Singapore/1/57/cx

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5

10

15

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20

25

30

Lys	Tyr	Thr	Ser	Gly	Arg	Gln	Glu	Lys	Asn	Pro	Ser	Leu	Arg	Met	Lys

35

40

45

Trp	Met	Met	Ala	Met	Lys	Tyr	Pro	Ile	Thr	Ala	Asp	Lys	Arg	Ile	Thr

50

55

60

Glu	Met	Ile	Pro	Glu	Arg	Asn	Glu	Gln	Gly	Gln	Thr	Leu	Trp	Ser	Lys

65

70

75

80

Met	Asn	Asp	Ala	Gly	Ser	Asp	Arg	Val	Met	Val	Ser	Pro	Leu	Ala	Val

85

90

95

Thr	Trp	Trp	Asn	Arg	Asn	Gly	Pro	Met	Thr	Ser	Thr	Val	His	Tyr	Pro

100

105

110

Lys	Ile	Tyr	Lys	Thr	Tyr	Phe	Glu	Lys	Val	Glu	Arg	Leu	Lys	His	Gly

115

120

125

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130

135

140

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SPECI

00-2008

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Asp Val Ile Met Glu Val Val Phe Pro Asn Glu Val Gly Ala Arg Ile
165 170 175

Leu Thr Ser Glu Ser Gln Leu Thr Thr Lys Glu Lys Lys Glu Glu
180 185 190

Leu Gin Asp Cys Lys Ile Ser Pro Leu Met Val Ala Tyr Met Leu Glu
195 200 205

Arg Glu Leu Val Arg Lys Thr Arg Phe Leu Pro Val Ala Gly Gly Thr
210 215 220

Ser Ser Val Tyr Ile Glu Val Leu His Leu Thr Gln Gly Thr Cys Trp
225 230 235 240

Glu Gln Met Tyr Thr Pro Gly Glu Val Arg Asn Asp Asp Val Asp
245 250 255

Gln Ser Leu Ile Ile Ala Ala Arg Asn Ile Val Arg Arg Ala Ala Val
260 265 270

Ser Ala Asp Pro Leu Ala Ser Leu Leu Glu Met Cys His Ser Thr Gln
275 280 285

Ile Gly Gly Thr Arg Met Val Asp Ile Leu Arg Gln Asn Pro Thr Glu
290 295 300

Glu Gln Ala Val Asp Ile Cys Lys Ala Met Gly Leu Arg Ile Ser
305 310 315 320

Ser Ser Phe Ser Phe Gly Gly Phe Thr Phe Lys Arg Thr Ser Gly Ser
325 330 335

Ser Val Lys Ile Glu Glu Val Leu Thr Gly Asn Leu Gln Thr Leu
340 345 350

Lys Ile Arg Val His Glu Gly Tyr Glu Glu Phe Thr Met Val Gly Lys
355 360 365

Arg Ala Thr Ala Ile Leu Arg Lys Ala Thr Arg Arg Leu Ile Gln Leu
370 375 380

Ile Val Ser Gly Arg Asp Glu Gln Ser Ile Ala Glu Ala Ile Ile Val
385 390 395 400

Printed 03/12/2001

SPECIMEN

00120896

Ala Met Val Phe Ser Gln Glu Asp Cys Met Ile Lys Ala Val Arg Gly
405 410 415

Asp Leu Asn Phe Val Asn Arg Ala Asn Gln Arg Leu Asn Pro Met His
420 425 430

Gln Leu Leu Arg His Phe Gln Lys Asp Ala Lys Val Leu Phe Gln Asn
435 440 445

Trp Gly Ile Glu His Ile Asp Asn Val Met Gly Met Ile Gly Val Leu
450 455 460

Pro Asp Met Thr Pro Ser Thr Glu Met Ser Met Arg Gly Val Arg Val
465 470 475 480

Ser Lys Met Gly Val Asp Glu Tyr Ser Ser Ala Glu Arg Val Val Val
485 490 495

Ser Ile Asp Arg Phe Leu Arg Val Arg Asp Gln Arg Gly Asn Val Leu
500 505 510

Leu Ser Pro Glu Glu Val Ser Glu Thr Gln Gly Thr Glu Lys Leu Thr
515 520 525

Ile Thr Tyr Ser Ser Met Met Trp Glu Ile Asn Gly Pro Glu Ser
530 535 540

Val Leu Val Asn Thr Tyr Gln Trp Ile Ile Arg Asn Trp Glu Thr Val
545 550 555 560

Lys Ile Gln Trp Ser Gln Asn Pro Thr Met Leu Tyr Asn Lys Met Glu
565 570 575

Phe Glu Pro Phe Gln Ser Leu Val Pro Lys Ala Ile Arg Gly Gln Tyr
580 585 590

Ser Gly Phe Val Arg Thr Leu Phe Gln Gln Met Arg Asp Val Leu Gly
595 600 605

Thr Phe Asp Thr Thr Gln Ile Ile Lys Leu Leu Pro Phe Ala Ala Ala
610 615 620

Pro Pro Lys Gln Ser Arg Met Gln Phe Ser Ser Leu Thr Val Asn Val
625 630 635 640

Arg Gly Ser Gly Met Arg Ile Leu Val Arg Gly Asn Ser Pro Val Phe
645 650 655

Printed 09-12-2001

SPECIMEN

081208

Asn Tyr Asn Lys Thr Thr Lys Arg Leu Thr Ile Leu Gly Lys Asp Ala
660 665 670

Gly Thr Leu Thr Glu Asp Pro Asp Glu Gly Thr Ser Gly Val Glu Ser
675 680 685

Ala Val Leu Arg Gly Phe Leu Ile Leu Gly Lys Glu Asp Arg Arg Tyr
690 695 700

Gly Pro Ala Leu Ser Ile Asn Glu Leu Ser Asn Leu Ala Lys Gly Glu
705 710 715 720

Lys Ala Asn Val Leu Ile Gly Gln Gly Asp Val Val Leu Val Met Lys
725 730 735

Arg Lys Arg Asp Ser Ser Ile Leu Thr Asp Ser Gln Thr Ala Thr Lys
740 745 750

Arg Ile Arg Met Ala Ile Asn Xaa Cys Xaa Ile Val Xaa Lys Arg Pro
755 760 765

Cys Phe Tyr
770

<210> 10
<211> 757
<212> PRT
<213> Influenza virus A/Singapore/1/57/ca

<400> 10
Met Asp Val Asn Pro Thr Leu Leu Phe Leu Lys Val Pro Ala Gln Asn
1 5 10 15

Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly Asp Pro Pro Tyr Ser His
20 25 30

Gly Thr Gly Thr Gly Tyr Thr Met Asp Thr Val Asn Arg Thr His Gln
35 40 45

Tyr Ser Glu Lys Gly Lys Trp Thr Thr Asn Thr Glu Thr Gly Ala Pro
50 55 60

Gln Leu Asn Pro Ile Asp Gly Pro Leu Pro Glu Asp Asn Glu Pro Ser
65 70 75 80

Gly Tyr Ala Gln Thr Asp Cys Val Leu Glu Ala Met Ala Phe Leu Glu

Printed 03-12-2005

SPECIES

20120698

85

90

95

Glu Ser His Pro Gly Ile Phe Glu Asn Ser Cys Leu Glu Thr Met Glu
 100 105 110

Val Ile Gln Gln Thr Arg Val Asp Lys Leu Thr Gln Gly Arg Gln Thr
 115 120 125

Tyr Asp Trp Thr Leu Asn Arg Asn Gln Pro Ala Ala Thr Ala Leu Ala
 130 135 140

Asn Thr Ile Glu Val Phe Arg Ser Asn Gly Leu Thr Ala Asn Glu Ser
 145 150 155 160

Gly Arg Leu Ile Asp Phe Leu Lys Asp Val Ile Glu Ser Met Asp Lys
 165 170 175

Glu Glu Met Glu Ile Thr Thr His Phe Gln Arg Lys Arg Arg Val Arg
 180 185 190

Asp Asn Met Thr Lys Lys Met Val Thr Gln Arg Thr Ile Gly Lys Lys
 195 200 205

Lys Gln Arg Leu Asn Lys Arg Ser Tyr Leu Ile Arg Ala Leu Thr Leu
 210 215 220

Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala
 225 230 235 240

Ile Ala Thr Pro Gly Met Gln Ile Arg Gly Phe Val Tyr Phe Val Glu
 245 250 255

Thr Leu Ala Arg Ser Ile Cys Glu Lys Leu Glu Gln Ser Gly Leu Pro
 260 265 270

Val Gly Gly Asn Glu Lys Lys Ala Lys Leu Ala Asn Val Val Arg Lys
 275 280 285

Met Met Thr Asn Ser Gln Asp Thr Glu Leu Ser Phe Thr Ile Thr Gly
 290 295 300

Asp Asn Thr Lys Trp Asn Glu Asn Gln Asn Pro Arg Met Phe Leu Ala
 305 310 315 320

Met Ile Thr Tyr Ile Thr Arg Asn Gln Pro Glu Trp Phe Arg Asn Val
 325 330 335

Leu Ser Ile Ala Pro Ile Met Phe Ser Asn Lys Met Ala Arg Leu Gly

	340	345	350
Lys Gly Tyr Met Phe Glu Ser Lys Ser Met Lys Ile Arg Thr Gln Ile			
355	360	365	
Pro Ala Glu Met Leu Ala Ser Ile Asp Leu Lys Tyr Phe Asn Glu Ser			
370	375	380	
Thr Arg Lys Lys Ile Glu Lys Ile Arg Pro Leu Leu Ile Asp Gly Thr			
385	390	395	400
Val Ser Leu Ser Pro Gly Met Met Met Gly Met Phe Asn Met Leu Ser			
405	410	415	
Thr Val Ile Gly Val Ser Ile Leu Asn Leu Gly Gln Lys Lys Tyr Thr			
420	425	430	
Lys Thr Thr Tyr Trp Trp Asp Gly Leu Gln Ser Ser Asp Asp Phe Ala			
435	440	445	
Leu Ile Val Asn Ala Pro Asn His Glu Gly Ile Gln Ala Gly Val Asp			
450	455	460	
Arg Phe Tyr Arg Thr Cys Lys Leu Val Gly Ile Asn Met Ser Lys Lys			
465	470	475	480
Lys Ser Tyr Ile Asn Arg Thr Gly Thr Phe Glu Phe Thr Ser Phe Phe			
485	490	495	
Tyr Arg Tyr Gly Phe Val Ala Asn Phe Ser Met Glu Leu Pro Ser Phe			
500	505	510	
Gly Val Ser Gly Ile Asn Glu Ser Ala Asp Met Ser Ile Gly Val Thr			
515	520	525	
Val Ile Lys Asn Asn Met Ile Asn Asn Asp Leu Gly Pro Ala Thr Ala			
530	535	540	
Gln Met Ala Leu Gln Leu Phe Ile Lys Asp Tyr Arg Tyr Thr Tyr Arg			
545	550	555	560
Cys His Arg Gly Asp Thr Gln Ile Gln Thr Arg Arg Ser Phe Glu Leu			
565	570	575	
Lys Lys Leu Trp Glu Gln Thr Arg Ser Lys Ala Gly Leu Leu Val Ser			
580	585	590	
Asp Gly Gly Pro Asn Leu Tyr Asn Ile Arg Asn Leu His Ile Pro Glu			

25-09-2000

biochemicals 12-2000

SPECIMEN

00120896

595

600

605

Val Cys Leu Lys Trp Gln Leu Met Asp Glu Asp Tyr Gln Gly Arg Leu
610 615 620

Cys Asn Pro Leu Asn Pro Phe Val Ser His Lys Glu Ile Glu Ser Val
625 630 635 640

Asn Asn Ala Val Val Met Pro Ala His Gly Pro Ala Lys Ser Met Glu
645 650 655

Tyr Asp Ala Val Ala Thr Thr His Ser Trp Ile Pro Lys Arg Asn Arg
660 665 670

Ser Ile Leu Asn Thr Ser Gln Arg Gly Ile Leu Glu Asp Glu Gln Met
675 680 685

Tyr Gln Lys Cys Cys Asn Leu Phe Glu Lys Phe Phe Pro Ser Ser Ser
690 695 700

Tyr Arg Arg Pro Val Gly Ile Ser Ser Met Val Glu Ala Met Val Ser
705 710 715 720

Arg Ala Arg Ile Asp Ala Arg Ile Asp Phe Glu Ser Gly Arg Ile Lys
725 730 735

Lys Glu Glu Phe Ala Glu Ile Met Lys Ile Cys Ser Thr Ile Glu Glu
740 745 750

Leu Arg Arg Gln Lys
755

<210> 11

<211> 716

<212> PRT

<213> Influenza virus A/Singapore/1/57/cb

<400> 11

Met Glu Asp Phe Val Arg Gln Cys Phe Asn Pro Met Ile Val Glu Leu
1 5 10 15

Ala Glu Arg Ala Met Lys Glu Tyr Gly Glu Asp Leu Lys Ile Glu Thr
20 25 30

Asn Lys Phe Ala Ala Ile Cys Thr His Leu Glu Val Cys Phe Met Tyr
35 40 45

Printed 08-12-2008

SPECIMEN

08-12-2008

Ser Asp Phe His Phe Ile Asn Glu Gln Gly Glu Ser Ile Ile Val Glu
50 55 60

Leu Asp Asp Pro Asn Ala Leu Leu Lys His Arg Phe Glu Ile Ile Glu
65 70 75 80

Gly Arg Asp Arg Thr Met Ala Trp Thr Val Val Asn Ser Ile Cys Asn
85 90 95

Thr Thr Gly Ala Glu Lys Pro Lys Phe Leu Pro Asp Leu Tyr Asp Tyr
100 105 110

Lys Glu Asn Arg Phe Ile Glu Ile Gly Val Thr Arg Arg Glu Val His
115 120 125

Ile Tyr Tyr Leu Glu Lys Ala Asn Lys Ile Lys Ser Glu Lys Thr His
130 135 140

Ile His Ile Phe Ser Phe Thr Gly Glu Glu Met Ala Thr Lys Ala Asp
145 150 155 160

Tyr Thr Leu Asp Glu Glu Ser Arg Ala Arg Ile Lys Thr Arg Leu Phe
165 170 175

Thr Ile Arg Gln Glu Met Ala Ser Arg Gly Leu Trp Asp Ser Phe Arg
180 185 190

Gln Ser Glu Arg Gly Glu Glu Thr Ile Glu Glu Arg Phe Glu Ile Thr
195 200 205

Gly Thr Met Arg Arg Leu Ala Asp Gln Ser Leu Pro Pro Asn Phe Ser
210 215 220

Cys Leu Glu Ile Phe Arg Ala Tyr Val Asp Gly Phe Glu Pro Asn Gly
225 230 235 240

Tyr Ile Glu Gly Lys Leu Ser Gln Met Ser Lys Glu Val Asn Ala Lys
245 250 255

Ile Glu Pro Phe Leu Lys Thr Thr Pro Arg Pro Ile Arg Leu Pro Asp
260 265 270

Gly Pro Pro Cys Ser Gln Arg Ser Lys Phe Leu Leu Met Asp Ala Leu
275 280 285

Lys Leu Ser Ile Glu Asp Pro Ser His Glu Gly Glu Gly Ile Pro Leu
290 295 300

Printed 09-12-2001

SPEC

09-12-2001

Tyr Asp Ala Ile Lys Cys Met Arg Thr Phe Phe Gly Trp Lys Glu Pro
 305 310 315 320

Tyr Val Val Lys Pro His Glu Lys Gly Ile Asn Pro Asn Tyr Leu Leu
 325 330 335

Ser Trp Lys Gln Val Leu Ala Glu Leu Gln Asp Ile Glu Asn Glu Glu
 340 345 350

Lys Ile Pro Arg Thr Lys Asn Met Lys Lys Thr Ser Gln Leu Lys Trp
 355 360 365

Ala Leu Gly Glu Asn Met Ala Pro Glu Lys Val Asp Phe Asp Asp Cys
 370 375 380

Arg Asp Ile Ser Asp Leu Lys Gln Tyr Asp Ser Asp Glu Pro Glu Leu
 385 390 395 400

Arg Ser Leu Ser Ser Trp Ile Gln Asn Glu Phe Asn Lys Ala Cys Glu
 405 410 415

Leu Thr Asn Ser Ile Trp Ile Glu Leu Asp Glu Ile Gly Glu Asp Val
 420 425 430

Ala Pro Ile Glu His Ile Ala Ser Met Arg Arg Asn Tyr Phe Thr Ala
 435 440 445

Glu Val Ser His Cys Arg Ala Thr Glu Tyr Ile Met Lys Gly Val Tyr
 450 455 460

Ile Asn Thr Ala Leu Leu Asn Ala Ser Cys Ala Ala Met Asp Asp Phe
 465 470 475 480

Gln Leu Ile Pro Met Ile Ser Lys Cys Arg Thr Lys Glu Gly Arg Arg
 485 490 495

Lys Thr Asn Leu Tyr Gly Phe Ile Val Lys Gly Arg Ser His Leu Arg
 500 505 510

Asn Asp Thr Asp Val Val Asn Phe Val Ser Met Glu Phe Ser Leu Thr
 515 520 525

Asp Pro Arg Leu Glu Pro His Lys Trp Glu Lys Tyr Cys Val Leu Glu
 530 535 540

Ile Gly Asp Met Leu Leu Arg Ser Ala Ile Gly Gln Val Ser Arg Pro
 545 550 555 560

Sequencies 2001

SPECIFIC

561208

Met Phe Leu Tyr Val Arg Thr Asn Gly Thr Ser Lys Ile Lys Met Lys
565 570 575

Trp Gly Met Glu Met Arg Arg Cys Leu Leu Gln Ser Leu Gln Gln Ile
580 585 590

Glu Ser Met Ile Glu Ala Gln Ser Ser Val Lys Glu Lys Asp Met Thr
595 600 605

Lys Glu Phe Phe Glu Asn Lys Ser Glu Thr Trp Pro Ile Gly Glu Ser
610 615 620

Pro Lys Gly Val Glu Glu Gly Ser Ile Gly Lys Val Cys Arg Thr Leu
625 630 635 640

Leu Ala Lys Ser Val Phe Asn Ser Leu Tyr Ala Ser Pro Gln Leu Glu
645 650 655

Gly Phe Ser Ala Glu Ser Arg Lys Leu Leu Leu Val Val Gln Ala Leu
660 665 670

Arg Asp Asn Leu Glu Pro Gly Thr Phe Asp Leu Gly Gly Leu Tyr Glu
675 680 685

Ala Ile Glu Glu Cys Leu Ile Asn Asp Pro Trp Val Leu Leu Asn Ala
690 695 700

Ser Trp Phe Asn Ser Phe Leu Thr His Ala Leu Arg
705 710 715

<210> 12

<211> 562

<212> PRT

<213> Influenza virus A/Singapore/1/57/ca

<400> 12

Met Ala Ile Ile Tyr Leu Ile Leu Leu Phe Thr Ala Val Arg Gly Asp
1 5 10 15

Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Lys Val Asp
20 25 30

Thr Ile Leu Glu Gln Asn Val Thr Val Thr His Ala Lys Asp Ile Leu
35 40 45

Glu Lys Thr His Asn Gly Lys Leu Cys Lys Leu Asn Gly Ile Pro Pro
50 55 60

Printed 09-12-2000

SPEC

06120896

Leu Glu Leu Gly Asp Cys Ser Ile Ala Gly Trp Leu Leu Gly Asn Pro
 65 70 75 80

 Glu Cys Asp Arg Leu Leu Ser Val Pro Glu Trp Ser Tyr Ile Met Glu
 85 90 95

 Lys Glu Asn Pro Arg Asp Gly Leu Cys Tyr Pro Gly Ser Phe Asn Asp
 100 105 110

 Tyr Glu Glu Leu Lys His Leu Leu Ser Ser Val Lys His Phe Glu Lys
 115 120 125

 Val Lys Ile Leu Pro Lys Asp Arg Trp Thr Gln His Thr Thr Gly
 130 135 140

 Gly Ser Arg Ala Cys Ala Val Ser Gly Asn Pro Ser Phe Phe Arg Asn
 145 150 155 160

 Met Val Trp Leu Thr Lys Glu Ser Asn Tyr Pro Val Ala Lys Gly
 165 170 175

 Ser Tyr Asn Asn Thr Ser Gly Glu Gln Met Leu Ile Ile Trp Gly Val
 180 185 190

 His His Pro Asn Asp Glu Thr Gln Arg Thr Leu Tyr Gln Asn Val
 195 200 205

 Gly Thr Tyr Val Ser Val Gly Thr Ser Thr Leu Asn Lys Arg Ser Thr
 210 215 220

 Pro Asp Ile Ala Thr Arg Pro Lys Val Asn Gly Leu Gly Ser Arg Met
 225 230 235 240

 Glu Phe Ser Trp Thr Leu Leu Asp Met Trp Asp Thr Ile Asn Phe Glu
 245 250 255

 Ser Thr Gly Asn Leu Ile Ala Pro Glu Tyr Gly Phe Lys Ile Ser Lys
 260 265 270

 Arg Gly Asn Ser Gly Ile Met Lys Thr Glu Gly Thr Leu Glu Asn Cys
 275 280 285

 Glu Thr Lys Cys Gln Thr Pro Leu Gly Ala Ile Asn Thr Thr Leu Pro
 290 295 300

 Phe His Asn Val His Pro Leu Thr Ile Gly Glu Cys Pro Lys Tyr Val
 305 310 315 320

Lys Ser Glu Lys Leu Val Ala Thr Gly Pro Arg Asn Val Pro Gln
325 330 335

Ile Glu Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Gly
340 345 350

Gly Trp Gln Gly Met Val Asp Gly Trp Tyr Gly Tyr His His Ser Asn
355 360 365

Asp Gln Gly Ser Gly Tyr Ala Ala Asp Lys Glu Ser Thr Gln Lys Ala
370 375 380

Phe Asp Gly Ile Thr Asn Lys Val Asn Ser Val Ile Glu Lys Met Asn
385 390 395 400

Thr Gln Phe Glu Ala Val Gly Lys Glu Phe Ser Asn Leu Glu Arg Arg
405 410 415

Leu Glu Asn Leu Asn Lys Lys Met Glu Asp Gly Phe Leu Asp Val Trp
420 425 430

Thr Tyr Asn Ala Glu Leu Leu Val Met Glu Asn Glu Arg Thr Leu
435 440 445

Asp Phe His Asp Ser Asn Val Lys Asn Leu Tyr Asp Lys Val Arg Met
450 455 460

Gln Leu Arg Asp Asn Val Lys Glu Leu Gly Asn Gly Cys Phe Glu Phe
465 470 475 480

Tyr His Lys Cys Asp Asp Glu Cys Met Asn Ser Val Lys Asn Gly Thr
485 490 495

Tyr Asp Tyr Pro Lys Tyr Glu Glu Ser Lys Leu Asn Arg Asn Glu
500 505 510

Ile Lys Gly Val Lys Leu Ser Ser Met Gly Val Tyr Gln Ile Leu Ala
515 520 525

Ile Tyr Ala Thr Val Ala Gly Ser Leu Ser Leu Ala Ile Met Met Ala
530 535 540

Gly Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
545 550 555 560

Cys Ile

Printed 03-09-2000

SPF

000126896

<210> 13

<211> 506

<212> PRT

<213> Influenza virus A/Singapore/1/57/ca

<400> 13

Met Ala Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Asp
1 5 10 15

Gly Glu Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Lys Met
20 25 30

Ile Asp Gly Ile Gly Arg Phe Tyr Ile Gln Met Cys Thr Glu Leu Lys
35 40 45

Leu Ser Asp Tyr Glu Gly Arg Leu Ile Gln Asn Ser Leu Thr Ile Glu
50 55 60

Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu
65 70 75 80

Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
85 90 95

Tyr Lys Arg Val Asn Gly Lys Trp Met Arg Glu Leu Val Leu Tyr Asp
100 105 110

Lys Glu Glu Ile Arg Arg Ile Trp Arg Gln Ala Asn Asn Gly Asp Asp
115 120 125

Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
130 135 140

Asp Thr Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
145 150 155 160

Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser
165 170 175

Gly Ala Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu
180 185 190

Leu Ile Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
195 200 205

Gly Glu Asn Gly Arg Lys Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn

Printed 05/12/2001

SPECIMEN

30012001

210

215

220

Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp
225 230 235 240

Gln Val Arg Glu Ser Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu
245 250 255

Ile Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
260 265 270

Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Thr Ala Val Ala Ser Gly
275 280 285

Tyr Asp Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe
290 295 300

Lys Leu Leu Gln Asn Ser Gln Val Tyr Ser Leu Ile Arg Pro Asn Glu
305 310 315 320

Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys Asn Ser Ala
325 330 335

Ala Phe Glu Asp Leu Arg Val Ser Ser Phe Ile Arg Gly Thr Lys Val
340 345 350

Ile Pro Arg Gly Lys Leu Ser Thr Arg Gly Val Gln Ile Ala Ser Asn
355 360 365

Glu Asn Met Asp Thr Met Glu Ser Ser Thr Leu Glu Leu Arg Ser Arg
370 375 380

Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Asn Gln Gln Arg
385 390 395 400

Ala Ser Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg
405 410 415

Asn Leu Pro Phe Asp Lys Thr Thr Ile Met Ala Ala Phe Thr Gly Asn
420 425 430

Ala Glu Gly Arg Thr Ser Asp Met Arg Ala Glu Ile Ile Arg Met Met
435 440 445

Glu Gly Ala Lys Pro Glu Glu Val Ser Phe Gln Gly Arg Gly Val Phe
450 455 460

Glu Leu Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp

346703-222603

SPEC

00120686

465

470

475

480

Met Ser Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Tyr
 485 490 495

Asp Asn Xaa Gly Lys Ile Pro Leu Phe Leu
 500 505

<210> 14

<211> 469

<212> PRT

<213> Influenza virus A/Singapore/1/97/ca

<400> 14

Met Asn Pro Asn Gln Lys Ile Ile Thr Ile Gly Ser Val Ser Leu Thr
 1 5 10 15

Ile Ala Thr Val Cys Phe Leu Met Gln Ile Ala Ile Leu Ala Thr Thr
 20 25 30

Val Thr Leu His Phe Lys Gln His Glu Cys Asp Ser Pro Ala Ser Asn
 35 40 45

Gln Val Met Pro Cys Glu Pro Ile Ile Ile Glu Arg Asn Ile Thr Glu
 50 55 60

Ile Val Tyr Leu Asn Asn Thr Thr Ile Glu Lys Glu Ile Cys Pro Glu
 65 70 75 80

Val Val Glu Tyr Arg Asn Trp Ser Lys Pro Gln Cys Gln Ile Thr Gly
 85 90 95

Phe Ala Pro Phe Ser Lys Asp Asn Ser Ile Arg Leu Ser Ala Gly Gly
 100 105 110

Asp Ile Trp Val Thr Arg Glu Pro Tyr Val Ser Cys Asp Pro Gly Lys
 115 120 125

Cys Tyr Gln Phe Ala Leu Gly Gln Gly Thr Thr Leu Tyr Asn Lys His
 130 135 140

Ser Asn Gly Thr Ile His Asp Arg Ile Pro His Arg Thr Leu Leu Met
 145 150 155 160

Asn Glu Leu Gly Val Pro Phe His Leu Gly Thr Lys Gln Val Cys Val
 165 170 175

Printed 02-12-2001

SPECIMEN

506203

Ala Trp Ser Ser Ser Cys His Asp Gly Lys Ala Trp Leu His Val
180 185 190

Cys Val Thr Gly Asp Asp Arg Asn Ala Thr Ala Ser Phe Ile Tyr Asp
195 200 205

Gly Arg Leu Val Asp Ser Ile Gly Ser Trp Ser Gln Asn Ile Leu Arg
210 215 220

Thr Gln Glu Ser Glu Cys Val Cys Ile Asn Gly Thr Cys Thr Val Val
225 230 235 240

Met Thr Asp Gly Ser Ala Ser Gly Arg Ala Asp Thr Arg Ile Leu Phe
245 250 255

Ile Lys Glu Gly Lys Ile Val Arg Ile Ser Pro Leu Ser Gly Ser Ala
260 265 270

Gln His Ile Glu Glu Cys Ser Cys Tyr Pro Arg Tyr Pro Asp Val Arg
275 280 285

Cys Ile Cys Arg Asp Asn Trp Lys Gly Ser Asn Arg Pro Val Ile Asp
290 295 300

Ile Asn Met Glu Asp Tyr Ser Ile Asp Ser Ser Tyr Val Cys Ser Gly
305 310 315 320

Leu Val Gly Asp Thr Pro Arg Asn Asp Asp Ser Ser Ser Asn Ser Asn
325 330 335

Cys Arg Asp Pro Asn Asn Glu Arg Gly Asn Pro Gly Val Lys Gly Trp
340 345 350

Ala Phe Asp Asn Gly Asp Asp Val Trp Met Gly Arg Thr Ile Asn Lys
355 360 365

Asp Ser Arg Ser Gly Tyr Glu Thr Phe Lys Val Ile Gly Gly Trp Ser
370 375 380

Thr Pro Asn Ser Lys Ser Gln Val Asn Arg Gln Val Ile Val Asp Asn
385 390 395 400

Asn Asn Trp Ser Gly Tyr Ser Gly Ile Phe Ser Val Glu Gly Lys Ser
405 410 415

Cys Ile Asn Arg Cys Phe Tyr Val Glu Leu Ile Arg Gly Arg Pro Gln
420 425 430

Printed 09/12/2000

SPEC

09/12/2000

Glu Thr Arg Val Trp Trp Thr Ser Asn Ser Ile Val Val Phe Cys Gly
438 440 445

Thr Ser Gly Thr Tyr Gly Thr Gly Ser Trp Pro Asp Gly Ala Asn Ile
450 455 460

Asn Phe Met Pro Ile
465

<210> 15

<211> 252

<212> PRF

<213> Influenza virus A/Singapore/1/57/ca

<400> 15

Met Ser Leu Leu Thr Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro
1 5 10 15

Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe
20 25 30

Ala Gly Lys Asn Thr Asp Leu Glu Ala Leu Met Glu Trp Leu Lys Thr
35 40 45

Arg Pro Ile Leu Ser Pro Leu Thr Lys Gly Ile Leu Gly Phe Val Phe
50 55 60

Thr Leu Thr Val Pro Ser Glu Arg Gly Leu Gln Arg Arg Phe Val
65 70 75 80

Gln Asn Ala Leu Asn Gly Asn Gly Asp Pro Asn Asn Met Asp Arg Ala
85 90 95

Val Lys Leu Tyr Lys Leu Lys Arg Glu Ile Thr Phe His Gly Ala
100 105 110

Lys Glu Ile Ala Leu Ser Tyr Ser Ala Gly Ala Leu Ala Ser Cys Met
115 120 125

Gly Leu Ile Tyr Asn Arg Met Gly Ala Val Thr Thr Glu Val Ala Phe
130 135 140

Gly Leu Val Cys Ala Thr Cys Glu Gln Ile Ala Asp Ser His His Arg
145 150 155 160

Ser His Arg Gln Met Val Thr Thr Asn Pro Leu Ile Arg His Glu
165 170 175

Printed 03-12-2004

SPECIMEN

061208

Asn Arg Met Val Leu Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met
180 185 190

Ala Gly Ser Ser Glu Gln Ala Ala Glu Ala Met Glu Val Ala Ser Gln
195 200 205

Ala Arg Gln Met Val Gln Ala Met Arg Ala Ile Gly Thr His Pro Ser
210 215 220

Ser Ser Ala Gly Leu Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr
225 230 235 240

Gln Lys Arg Met Gly Val Gln Met Gln Arg Phe Lys
245 250

<210> 16

<211> 97

<212> PRT

<213> Influenza virus A/Singapore/1/57/ca

<400> 16

Met Ser Leu Leu Thr Glu Val Glu Thr Pro Ile Arg Asn Glu Trp Gly
1 5 10 15

Cys Arg Cys Asn Asp Ser Ser Asp Pro Leu Val Val Ala Ala Ser Ile
20 25 30

Ile Gly Ile Leu His Leu Ile Leu Trp Ile Leu Asp Arg Leu Phe Phe
35 40 45

Lys Cys Ile Tyr Arg Phe Phe Lys His Gly Leu Lys Arg Gly Pro Ser
50 55 60

Thr Glu Gly Val Pro Glu Ser Met Arg Glu Glu Tyr Arg Lys Glu Gln
65 70 75 80

Gln Ser Ala Val Asp Ala Asp Asp Ser His Phe Val Ser Ile Glu Leu
85 90 95

Glu

<210> 17

<211> 237

<212> PRT

Printed 03-12-2005

SECRET

00120307

<213> Influenza virus A/Singapore/1/57/cu

<400> 17

Met Asp Pro Asn Thr Val Ser Ser Phe Gln Val Asp Cys Phe Leu Trp
1 5 10 15

His Val Arg Lys Gln Val Ala Asp Gln Glu Leu Gly Asp Ala Pro Phe
20 25 30

Leu Asp Arg Leu Arg Arg Asp Gln Lys Ser Leu Arg Gly Arg Gly Ser
35 40 45

Thr Leu Gly Leu Asn Ile Glu Thr Ala Thr Arg Val Gly Lys Gln Ile
50 55 60

Val Glu Arg Ile Leu Lys Glu Glu Ser Asp Glu Ala Leu Lys Met Thr
65 70 75 80

Met Ala Ser Ala Pro Ala Ser Arg Tyr Leu Thr Asp Met Thr Ile Glu
85 90 95

Glu Met Ser Arg Asp Trp Phe Met Leu Met Pro Lys Gln Lys Val Ser
100 105 110

Gly Pro Leu Cys Ile Arg Met Asp Gln Ala Ile Met Asp Lys Asn Ile
115 120 125

Ile Leu Lys Ala Asn Phe Ser Val Ile Phe Asp Arg Leu Glu Thr Leu
130 135 140

Ile Leu Leu Arg Ala Phe Thr Glu Glu Gly Ala Ile Val Gly Glu Ile
145 150 155 160

Ser Pro Leu Pro Ser Leu Pro Gly His Thr Asn Glu Asp Val Lys Asn
165 170 175

Ala Ile Gly Val Leu Ile Gly Leu Glu Trp Asn Asp Asn Thr Val
180 185 190

Arg Val Ser Lys Thr Leu Gln Arg Phe Ala Trp Arg Asn Ser Asn Glu
195 200 205

Asn Gly Arg Pro Pro Leu Thr Pro Lys Gln Lys Arg Lys Met Ala Arg
210 215 220

Thr Ile Arg Ser Lys Val Arg Arg Asn Lys Met Ala Asp
225 230 235

Printed: 03/12/2001

SPEC

00263

<210> 18

<211> 121

<212> PRT

<213> Influenza virus A/Singapore/1/57/ca

<400> 18

Met Asp Pro Asn Thr Val Ser Ser Phe Gln Asp Ile Leu Met Arg Met
1 5 10 15

Ser Lys Met Gln Leu Gly Ser Ser Ser Glu Asp Leu Asn Gln Gly Met Ile
20 25 30

Thr Gln Phe Glu Ser Leu Lys Leu Tyr Arg Asp Ser Leu Gly Glu Thr
35 40 45

Val Met Arg Met Gly Asp Leu His Ser Leu Gln Asn Arg Asn Gly Lys
50 55 60

Trp Arg Glu Gln Leu Gly Gln Lys Phe Glu Glu Ile Arg Trp Leu Ile
65 70 75 80

Glu Glu Val Arg His Lys Leu Lys Ile Thr Glu Asn Ser Phe Glu Gln
85 90 95

Ile Thr Phe Met Gln Ala Leu Gln Leu Leu Phe Glu Val Glu Gln Glu
100 105 110

Ile Arg Thr Phe Ser Phe Gln Leu Ile
115 120

<210> 19

<211> 2396

<212> DNA

<213> Influenza B/Vienna/1/99/ca

<400> 19

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taaggcacaa tgaagccaaa acgtattga aacaaacaaac agttagatcaa tataacataa 120
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<211> 2369

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<213> Influenza B/Vienna/1/99/ca

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09.09.2001

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<211> 1882

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<210> 25

<211> 1190

<212> DNA

<213> Influenza B/Vienna/1/99/ca

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agatagaaga atgcattaa attcattttt tctgttattt ctatctatgc atttaaagcaaa 1140
atgttgcataa atgtcgcgaa ataaaactggaa aaaagtgcgt ttttttctact 1190

<210> 26:

<211> 1097

<212> DNA

<213> Influenza B/Vienna/1/99/ca

<400> 26

agcagaagca gagcattgtt ttagtcaactg gcaaacagga aaaatggcga acaaacataac 60
cacaacacaa attgggggg gtcggggagc aaccaatgcc accataaaact ttgaaacagg 120
aatttgttag tgctatgeaa ggcttcatg gcaaaagagcc cttgactacc ctggtaaga 180
ccgcctaaac agactazaga gaaaattaga gcaagaga aagactcaca acaaaaagtga 240
gcctgaaagt aaaaggatgt ctcttgaaga gaggaaagca attggagtaa aaatgtgaa 300
agtaactccca tttagtgcatttgcgtgg aartgaaggg tttagccat actatatgaa 360
aagttootca aatagcaact gtcggaaata caattggacc gattaccctt caacaccagg 420
gaggtgcctt gatgacatag aagaagaacc agggatgtt gatggcccaa ctgaaatagt 480
attaaggcac atgaaczaa aagatgcaag gaaaaagata aaagaggaag taaacactca 540
gaaagaaggg aagtccgtt tgacaataaa aaggatata cgtaatgtat tgcttgcag 600
agtgttggta aacggaaacat tcctcaaaaca ccccaatggc tacaagtct tatcaactct 660
gcatagatg aatgcataatg accagagtgg aaggtctgtt gctaaccctt ttagtcaactg 720
tgatettaca gtggaggatg aagaagatgg ccateggatc otcaactcac tcttcgagcg 780
tcttaatgaa ggacattcaa agccaatttg agcagctgaa actggggatgg gagtcttatac 840
ccaatttgtt caagagcacc gattatcacc &gaagaggga gacaattaaa ctggtaacag 900
aagaacttta tcttttaagt aaaagaatttgg atgataacat attgtccac aaaacagtaa 960
tagctaaacag ctccataata gctgacatgg ttgratcatt atcattattt gaaacattgt 1020
atgaaatgaa ggatgtgggtt gaagtgcaca gcaggcagtg ctttgtgaatt taaaataaa 1080
atccctttgt tactact 1097

Printed 03-12-2004

SPECI

00020896

<210> 27

<211> 770

<212> PRT

<213> Influenza B/Vienna/1/99/c2

<400> 27

Met Thr Leu Ala Lys Ile Glu Leu Leu Lys Gln Leu Leu Arg Asp Asn
1 5 10 15

Glu Ala Lys Thr Val Leu Lys Gln Thr Thr Val Asp Gln Tyr Asn Ile
26 25 30

Ile Arg Lys Phe Asn Thr Ser Arg Ile Glu Lys Asn Pro Ser Leu Arg
35 40 45

Met Lys Trp Ala Met Cys Ser Asn Phe Pro Leu Ala Leu Thr Lys Gly
50 55 60

Asp Met Ala Asn Arg Ile Pro Leu Glu Tyr Lys Gly Ile Gln Leu Lys
65 70 75 80

Thr Asn Ala Glu Asp Ile Gly Thr Lys Gly Gln Met Cys Ser Ile Ala
85 90 95

Ala Val Thr Trp Trp Asn Thr Tyr Gly Pro Ile Gly Asp Thr Glu Gly
100 105 110

Phe Glu Lys Val Tyr Glu Ser Phe Phe Leu Arg Lys Met Arg Leu Asp
115 120 125

Asn Ala Thr Trp Gly Arg Ile Thr Phe Gly Pro Val Glu Arg Val Arg
130 135 140

Lys Arg Val Leu Leu Asn Pro Leu Thr Lys Glu Met Pro Pro Asp Glu
145 150 155 160

Ala Ser Asn Val Ile Met Glu Ile Leu Phe Pro Lys Glu Ala Gly Ile
165 170 175

Pro Arg Glu Ser Thr Trp Ile His Arg Glu Leu Ile Lys Glu Lys Arg
180 185 190

Glu Lys Leu Lys Gly Thr Met Ile Thr Pro Ile Val Leu Ala Tyr Met
195 200 205

Leu Glu Arg Glu Leu Val Ala Arg Arg Arg Phe Leu Pro Val Ala Gly
210 215 220

Printed 03-22-2001

SPECIMEN

10012001

Ala Thr Ser Ala Glu Phe Ile Glu Met Leu His Cys Leu Gln Gly Glu
225 230 235 240

Asn Trp Arg Gln Ile Tyr His Pro Gly Gly Asn Lys Leu Thr Glu Ser
245 250 255

Arg Ser Gln Ser Met Ile Val Ala Cys Arg Lys Ile Ile Arg Arg Ser
260 265 270

Ile Val Ala Ser Asn Pro Leu Glu Leu Ala Val Glu Ile Ala Asn Lys
275 280 285

Thr Val Ile Asp Thr Glu Pro Leu Lys Ser Cys Leu Thr Ala Ile Asp
290 295 300

Gly Gly Asp Val Ala Cys Asp Ile Ile Arg Ala Ala Leu Gly Leu Lys
305 310 315 320

Ile Arg Gln Arg Gln Arg Phe Gly Arg Leu Glu Leu Lys Arg Ile Ser
325 330 335

Gly Arg Gly Phe Lys Asn Asp Glu Glu Ile Leu Ile Gly Asn Gly Thr
340 345 350

Ile Gln Lys Ile Gly Ile Trp Asp Gly Glu Glu Phe His Val Arg
355 360 365

Cys Gly Glu Cys Arg Gly Ile Leu Lys Lys Ser Lys Met Arg Met Glu
370 375 380

Lys Leu Leu Ile Asn Ser Ala Lys Lys Glu Asp Met Lys Asp Leu Ile
385 390 395 400

Ile Leu Cys Met Val Phe Ser Gln Asp Thr Arg Met Phe Gln Gly Val
405 410 415

Arg Gly Glu Ile Asn Phe Leu Asn Arg Ala Gly Gln Leu Leu Ser Pro
420 425 430

Met Tyr Gln Leu Gln Arg Tyr Phe Leu Asn Arg Ser Asn Asp Leu Phe
435 440 445

Asp Gln Trp Gly Tyr Glu Glu Ser Pro Lys Ala Ser Glu Leu His Gly
450 455 460

Ile Asn Glu Leu Met Asn Ala Ser Asp Tyr Thr Leu Lys Gly Val Val
465 470 475 480

Printed 03/22/2004

SREG

00120896

Val Thr Lys Asn Val Ile Asp Asp Phe Ser Ser Thr Glu Thr Glu Lys
 485 490 495

Val Ser Ile Thr Lys Asn Leu Ser Leu Ile Lys Arg Thr Gly Glu Val
 500 505 510

Ile Met Gly Ala Asn Asp Val Ser Glu Leu Glu Ser Gln Ala Gln Leu
 515 520 525

Met Ile Thr Tyr Asp Thr Pro Lys Met Trp Glu Met Gly Thr Thr Lys
 530 535 540

Glu Leu Val Gln Asn Thr Tyr Gln Trp Val Leu Lys Asn Leu Val Thr
 545 550 555 560

Leu Lys Ala Gln Phe Leu Leu Gly Lys Glu Asp Met Phe Gln Trp Asp
 565 570 575

Ala Phe Glu Ala Phe Glu Ser Ile Ile Pro Gln Lys Met Ala Gly Gln
 580 585 590

Tyr Ser Gly Phe Ala Arg Ala Val Leu Lys Gln Met Arg Asp Gln Glu
 595 600 605

Val Met Lys Thr Asp Gln Phe Ile Lys Leu Leu Pro Phe Cys Phe Ser
 610 615 620

Pro Pro Lys Leu Arg Ser Asn Gln Gly Glu Pro Tyr Gln Phe Leu Arg Leu
 625 630 635 640

Val Leu Lys Gly Gly Glu Asn Phe Ile Glu Val Arg Lys Gly Ser
 645 650 655

Pro Leu Phe Ser Tyr Asn Pro Gln Thr Glu Val Leu Thr Ile Cys Gly
 660 665 670

Arg Met Met Ser Leu Lys Gly Lys Ile Gln Asp Glu Glu Arg Asn Arg
 675 680 685

Ser Met Gly Asn Ala Val Leu Ala Gly Phe Leu Val Ser Gly Lys Tyr
 690 695 700

Asp Pro Asp Leu Gly Asp Phe Lys Thr Ile Glu Glu Leu Glu Lys Leu
 705 710 715 720

Lys Pro Gly Glu Lys Ala Asn Ile Leu Leu Tyr Gln Gly Lys Pro Val
 725 730 735

Printed 09-12-2001

SPECIMEN

09-12-2001

Lys Val Val Lys Arg Lys Arg Tyr Ser Ala Leu Ser Asn Asp Ile Ser
740 745 750

Gln Gly Ile Lys Arg Gln Arg Met Thr Val Glu Ser Met Gly Trp Ala
755 760 765

Leu Ser
770

<210> 28

<211> 752

<212> PRT

<213> Influenza B/Vienna/1/99/ca

<400> 28

Met Asn Ile Asn Pro Tyr Phe Leu Phe Ile Asp Val Pro Ile Gln Ala
1 5 10 15

Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly Val Pro Pro Tyr Ser His
20 25 30

Gly Thr Gly Thr Gly His Thr Ile Asp Thr Val Ile Arg Thr His Glu
35 40 45

Tyr Ser Asn Lys Gly Lys Gln Tyr Val Ser Asp Ile Thr Gly Cys Thr
50 55 60

Met Val Asp Pro Thr Asn Gly Pro Leu Pro Glu Asp Asn Glu Pro Ser
65 70 75 80

Ala Tyr Ala Gln Leu Asp Cys Val Leu Glu Ala Leu Asp Arg Met Asp
85 90 95

Glu Glu His Pro Gly Leu Phe Gln Ala Ala Ser Gln Asn Ala Met Glu
100 105 110

Ala Leu Met Val Thr Thr Val Asp Lys Leu Thr Gln Gly Arg Gln Thr
115 120 125

Phe Asp Trp Thr Val Cys Arg Asn Gln Pro Ala Ala Thr Ala Leu Asn
130 135 140

Thr Thr Ile Thr Ser Phe Arg Leu Asn Asp Leu Asn Gly Ala Asp Lys
145 150 155 160

Gly Gly Leu Val Pro Phe Cys Gln Asp Ile Ile Asp Ser Leu Asp Lys
165 170 175

Printed 03-22-2007

SPECI

00020896

Pro Glu Met Thr Phe Phe Ser Val Lys Asn Ile Lys Lys Lys Phe Pro
180 185 190

Ala Lys Asn Arg Lys Gly Phe Leu Ile Lys Arg Ile Pro Met Lys Val
195 200 205

Lys Asp Arg Ile Ser Arg Val Glu Tyr Ile Lys Arg Ala Leu Ser Leu
210 215 220

Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala
225 230 235 240

Ile Ala Thr Ala Gly Ile Gln Ile Arg Gly Phe Val Leu Val Val Glu
245 250 255

Asn Leu Ala Lys Asn Ile Cys Glu Asn Leu Glu Gln Ser Gly Leu Pro
260 265 270

Val Gly Asn Glu Lys Lys Ala Lys Leu Ser Asn Ala Val Ala Lys
275 280 285

Met Leu Ser Asn Cys Pro Pro Gly Gly Ile Ser Met Thr Val Thr Gly
290 295 300

Asp Asn Thr Lys Trp Asn Glu Cys Leu Asn Pro Arg Val Phe Leu Ala
305 310 315 320

Met Thr Glu Arg Ile Thr Arg Asp Ser Pro Ile Trp Phe Arg Asp Phe
325 330 335

Cys Ser Ile Ala Pro Val Leu Phe Ser Asn Lys Ile Ala Arg Leu Gly
340 345 350

Lys Gly Phe Met Ile Thr Ser Lys Thr Lys Arg Leu Lys Ala Gln Ile
355 360 365

Pro Cys Pro Asp Leu Phe Ser Ile Pro Leu Glu Arg Tyr Asn Glu Glu
370 375 380

Thr Arg Ala Lys Leu Lys Lys Leu Lys Pro Phe Phe Asn Glu Glu Gly
385 390 395 400

Thr Ala Ser Leu Ser Pro Gly Met Met Gly Met Phe Asn Met Leu
405 410 415

Ser Thr Val Leu Gly Val Ala Ala Leu Gly Ile Lys Asn Ile Gly Asn
420 425 430

Printed: 03-12-2001

SPES

001268C

Lys Glu Tyr Leu Trp Asp Gly Leu Gln Ser Ser Asp Asp Phe Ala Leu
435 440 445

Phe Val Asn Ala Lys Asp Glu Glu Thr Cys Met Glu Gly Ile Asn Asp
450 455 460

Pha Tyr Arg Thr Cys Lys Leu Leu Gly Ile Asn Met Ser Lys Lys Lys
465 470 475 480

Ser Tyr Cys Asn Glu Thr Gly Met Phe Glu Phe Thr Ser Met Phe Tyr
485 490 495

Arg Asp Gly Phe Val Ser Asn Phe Ala Met Glu Ile Pro Ser Phe Gly
500 505 510

Val Ala Gly Val Asn Glu Ser Ala Asp Met Ala Ile Gly Met Thr Ile
515 520 525

Ile Lys Asn Asn Met Ile Asn Asn Gly Met Gly Pro Ala Thr Ala Gln
530 535 540

Thr Ala Ile Gln Leu Phe Ile Ala Asp Tyr Arg Tyr Thr Tyr Lys Cys
545 550 555 560

His Arg Gly Asp Ser Lys Val Glu Gly Lys Arg Met Lys Ile Ile Lys
565 570 575

Glu Leu Trp Glu Asn Thr Lys Gly Arg Asp Gly Leu Leu Val Ala Asp
580 585 590

Gly Gly Pro Asn Ile Tyr Asn Leu Arg Asn Leu His Ile Pro Glu Ile
595 600 605

Val Leu Lys Tyr Asn Leu Met Asp Pro Glu Tyr Lys Gly Arg Leu Leu
610 615 620

His Pro Gln Asn Pro Phe Val Gly His Leu Ser Ile Glu Gly Ile Lys
625 630 635 640

Glu Ala Asp Ile Thr Pro Ala His Gly Pro Val Lys Lys Met Asp Tyr
645 650 655

Asp Ala Val Ser Gly Thr His Ser Trp Arg Thr Lys Arg Asn Arg Ser
660 665 670

Ile Leu Asn Thr Asp Gln Arg Asn Met Ile Leu Glu Glu Gln Cys Tyr
675 680 685

Printed 03/22/2000

SPECIMEN

60120896

Ala Lys Cys Cys Asn Leu Phe Glu Ala Cys Phe Asn Ser Ala Ser Tyr
690 695 700

Arg Lys Pro Val Gly Gln His Ser Met Leu Glu Ala Met Ala His Arg
705 710 715 720

Leu Arg Met Asp Ala Arg Leu Asp Tyr Glu Ser Gly Arg Met Ser Lys
725 730 735

Asp Asp Phe Glu Lys Ala Met Ala His Leu Gly Glu Ile Gly Tyr Thr
740 745 750

<210> 29
<211> 726
<212> PRT
<213> Influenza B/Vienna/1/99/oa

<400> 29
Met Asp Thr Phe Ile Thr Arg Asn Phe Gln Thr Thr Ile Ile Gln Lys
1 5 10 15

Ala Lys Asn Thr Met Ala Glu Phe Ser Glu Asp Pro Glu Leu Gln Pro
20 25 30

Ala Met Leu Phe Asn Ile Cys Val His Leu Glu Val Cys Tyr Val Ile
35 40 45

Ser Asp Met Asn Phe Leu Asp Glu Gln Gly Lys Ala Tyr Thr Ala Leu
50 55 60

Glu Gln Gln Gly Lys Glu Gln Asn Leu Arg Pro Gln Tyr Glu Val Ile
65 70 75 80

Glu Gln Met Pro Arg Thr Ile Ala Trp Met Val Gln Arg Ser Leu Ala
85 90 95

Gln Glu His Gly Ile Glu Thr Pro Lys Tyr Leu Ala Asp Leu Phe Asp
100 105 110

Tyr Lys Thr Lys Arg Phe Ile Glu Val Gly Ile Thr Lys Gly Leu Ala
115 120 125

Asp Asp Tyr Phe Trp Lys Lys Glu Lys Leu Gly Asn Ser Met Glu

130	135	140
Leu Met Ile Phe Ser Tyr Asn Gln Asp Tyr Ser Leu Ser Asn Glu Ser		
145	150	155
Ser Leu Asp Glu Glu Gly Lys Gly Arg Val Leu Ser Arg Leu Thr Glu		
165	170	175
Leu Gln Ala Glu Leu Ser Leu Lys Asn Leu Trp Gln Val Leu Ile Gly		
180	185	190
Glu Glu Asp Val Glu Lys Gly Ile Asp Phe Lys Leu Gly Gln Thr Ile		
195	200	205
Ser Arg Leu Arg Asp Ile Ser Val Pro Ala Gly Phe Ser Asn Phe Glu		
210	215	220
Gly Met Arg Ser Tyr Ile Asp Asn Ile Asp Pro Lys Gly Ala Ile Glu		
225	230	235
Arg Asn Leu Ala Arg Met Ser Pro Leu Val Ser Val Thr Pro Lys Lys		
245	250	255
Leu Lys Trp Glu Asp Leu Arg Pro Ile Gly Pro His Ile Tyr Asn His		
260	265	270
Glu Leu Pro Glu Val Pro Tyr Asn Ala Phe Leu Leu Met Ser Asp Glu		
275	280	285
Leu Gly Leu Ala Asn Met Thr Glu Gly Lys Ser Lys Lys Pro Lys Thr		
290	295	300
Leu Ala Lys Glu Cys Leu Glu Lys Tyr Ser Thr Leu Arg Asp Gln Thr		
305	310	315
Asp Pro Ile Leu Ile Met Lys Ser Glu Lys Ala Asn Glu Asn Phe Leu		
325	330	335
Trp Lys Leu Trp Arg Asp Cys Val Asn Thr Ile Ser Asn Glu Glu Met		
340	345	350
Ser Asn Glu Leu Gln Lys Thr Asn Tyr Ala Lys Trp Ala Thr Gly Asp		
355	360	365
Gly Leu Thr Tyr Gln Lys Ile Met Lys Glu Val Ala Ile Asp Asp Glu		
370	375	380
Thr Met Cys Gln Glu Glu Pro Lys Ile Pro Asn Lys Cys Arg Val Ala		

385	390	395	400
Ala Trp Val Gln Thr Glu Met Asn Leu Leu Ser Thr Leu Thr Ser Lys			
405	410	415	
Lys Ala Leu Asp Leu Pro Glu Ile Gly Pro Asp Val Ala Pro Val Glu			
420	425	430	
His Val Gly Ser Glu Arg Arg Lys Tyr Phe Val Asn Glu Ile Asn Tyr			
435	440	445	
Cys Lys Ala Ser Thr Val Met Met Lys Tyr Val Leu Phe His Thr Ser			
450	455	460	
Leu Leu Asn Glu Ser Asn Ala Ser Met Gly Lys Tyr Lys Val Ile Pro			
465	470	475	480
Ile Thr Asn Arg Val Val Asn Glu Gly Glu Ser Phe Asp Met Leu			
485	490	495	
Tyr Gly Leu Ala Val Lys Gly Gln Ser His Leu Arg Gly Asp Thr Asp			
500	505	510	
Val Val Thr Val Val Thr Phe Glu Phe Ser Ser Thr Asp Pro Arg Val			
515	520	525	
Asp Ser Gly Lys Trp Pro Lys Tyr Thr Val Phe Arg Ile Gly Ser Leu			
530	535	540	
Phe Val Ser Gly Arg Glu Lys Ser Val Tyr Leu Tyr Cys Arg Val Asn			
545	550	555	560
Gly Thr Asn Lys Ile Gln Met Lys Trp Gly Met Glu Ala Arg Arg Cys			
565	570	575	
Leu Leu Gln Ser Met Gln Gln Met Glu Ala Ile Val Glu Gln Glu Ser			
580	585	590	
Ser Ile Gln Gly Tyr Asp Met Thr Lys Ala Cys Phe Lys Gly Asp Arg			
595	600	605	
Val Asn Ser Pro Lys Thr Phe Ser Ile Gly Thr Gln Glu Gly Lys Leu			
610	615	620	
Val Lys Gly Ser Phe Gly Lys Ala Leu Arg Val Ile Phe Thr Lys Cys			
625	630	635	640
Leu Met His Tyr Val Phe Gly Asn Ala Gln Leu Glu Gly Phe Ser Ala			

Printed 03-12-2001

SPECIEST

0012089

645 650 655

Glu Ser Arg Arg Leu Leu Leu Ile Gln Ala Leu Lys Asp Arg Lys
660 665 670

Gly Pro Trp Val Phe Asp Leu Glu Gly Met Tyr Ser Gly Ile Gln Glu
675 680 685

Cys Ile Ser Asn Asn Pro Trp Val Ile Gln Ser Ala Tyr Trp Phe Asn
690 695 700

Glu Trp Leu Gly Phe Glu Lys Glu Gly Ser Lys Val Leu Glu Ser Val
705 710 715 720

Asp Glu Ile Met Asp Glu
725

<210> 30

<211> 384

<212> PRT

<213> Influenza B/Vienna/1/99/ca

<400> 30

Met Lys Ala Ile Ile Val Leu Leu Met Val Val Thr Ser Asn Ala Asp
1 5 10 15

Arg Ile Cys Thr Gly Ile Thr Ser Ser Asn Ser Pro His Val Val Lys
20 25 30

Thr Ala Thr Gln Gly Glu Val Asn Val Thr Gly Ala Ile Pro Leu Thr
35 40 45

Thr Thr Pro Thr Lys Ser His Phe Ala Asn Leu Lys Gly Thr Lys Thr
50 55 60

Arg Gly Lys Leu Cys Pro Thr Cys Leu Asn Cys Thr Asp Leu Asp Val
65 70 75 80

Ala Leu Gly Arg Pro Met Cys Val Gly Ile Thr Pro Ser Ala Lys Ala
85 90 95

Ser Ile Leu His Glu Val Arg Pro Val Thr Ser Gly Cys Phe Pro Ile
100 105 110

Met His Asp Arg Thr Lys Ile Arg Gln Leu Pro Asn Leu Leu Arg Gly
115 120 125

Tyr Glu Lys Ile Arg Leu Ser Thr Gln Asn Val Ile Asn Thr Glu Lys
 130 135 140
 Ala Pro Gly Gly Pro Tyr Arg Leu Gly Thr Ser Gly Ser Cys Pro Asn
 145 150 155 160
 Ala Thr Ser Lys Ser Gly Phe Phe Ala Thr Met Ala Trp Ala Val Pro
 165 170 175
 Arg Asp Asn Asn Lys Thr Ala Thr Asn Pro Leu Thr Val Glu Val Pro
 180 185 190
 His Ile Cys Thr Lys Glu Glu Asp Gln Ile Thr Val Trp Gly Phe His
 195 200 205
 Ser Asp Asn Asn Lys Thr Gln Met Lys Asn Leu Tyr Gly Asp Ser Asn Pro
 210 215 220
 Gln Lys Phe Thr Ser Ser Ala Asn Gly Ile Thr Thr His Tyr Val Ser
 225 230 235 240
 Gln Ile Gly Gly Phe Pro Asp Gln Thr Glu Asp Gly Gly Leu Pro Gln
 245 250 255
 Ser Gly Arg Ile Val Val Asp Tyr Met Val Gln Lys Pro Gly Lys Thr
 260 265 270
 Gly Thr Ile Val Tyr Gln Arg Gly Ile Leu Leu Pro Gln Lys Val Trp
 275 280 285
 Cys Ala Ser Gly Arg Ser Lys Val Ile Lys Gly Ser Leu Pro Leu Ile
 290 295 300
 Gly Glu Ala Asp Cys Leu His Glu Lys Tyr Gly Gly Leu Asn Lys Ser
 305 310 315 320
 Lys Pro Tyr Tyr Thr Gly Glu His Ala Lys Ala Ile Gly Asn Cys Pro
 325 330 335
 Ile Trp Val Lys Thr Pro Leu Lys Leu Ala Asn Gly Thr Lys Tyr Arg
 340 345 350
 Pro Pro Ala Lys Leu Leu Lys Glu Arg Gly Phe Phe Gly Ala Ile Ala
 355 360 365
 Gly Phe Leu Glu Gly Gly Trp Glu Gly Met Ile Ala Gly Trp His Gly
 370 375 380

Printed 03/22/2001

SPECIMEN

00172689

Tyr Thr Ser His Gly Ala His Gly Val Ala Val Ala Ala Asp Ieu Lys
385 390 395 400

Ser Thr Gln Glu Ala Ile Asn Lys Ile Thr Lys Asn Leu Asn Ser Leu
405 410 415

Ser Glu Leu Glu Val Asn Asn Leu Gln Arg Leu Ser Gly Ala Met Asp
420 425 430

Glu Leu His Asn Gln Ile Leu Glu Leu Asp Glu Lys Val Asp Asp Leu
435 440 445

Arg Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu Ser
450 455 460

Asn Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu Glu
465 470 475 480

Arg Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Asp Ile Gly Asn
485 490 495

Gly Cys Phe Gln Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp Arg
500 505 510

Ile Ala Ala Gly Thr Phe Asn Ala Glu Glu Phe Ser Leu Pro Thr Phe
515 520 525

Asp Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu Asp
530 535 540

Asn His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu Ala
545 550 555 560

Val Thr Leu Met Ile Ala Ile Phe Ile Val Tyr Met Ile Ser Arg Asp
565 570 575

Asn Val Ser Cys Ser Ile Cys Leu
580

<210> 31

<211> 560

<212> PRT

<213> Influenza B/Vienna/1/99/cs

<400> 31

Met Ser Asn Met Asp Ile Asp Gly Ile Asn Thr Gly Thr Ile Asp Lys
1 5 10 15

Printed 06-12-2001

SPECIES

00420296

Thr Pro Glu Glu Ile Thr Phe Gly Thr Ser Gly Thr Thr Arg Pro Ile
20 25 30

Ile Arg Pro Ala Thr Leu Ala Pro Pro Ser Asn Lys Arg Thr Arg Asn
35 40 45

Pro Ser Pro Glu Arg Ala Thr Thr Ser Ser Glu Ala Asp Val Gly Arg
50 55 60

Lys Thr Gln Lys Lys Gln Thr Pro Thr Glu Ile Lys Lys Ser Val Tyr
65 70 75 80

Asn Met Val Val Lys Leu Gly Glu Phe Tyr Asn Gln Met Met Val Lys
85 90 95

Ala Gly Leu Asn Asp Asp Met Glu Arg Asn Leu Ile Gln Asn Ala Sis
100 105 110

Ala Val Glu Arg Ile Leu Leu Ala Ala Thr Asp Asp Lys Lys Thr Glu
115 120 125

Phe Gln Lys Lys Asn Thr Arg Asp Val Lys Glu Gly Lys Glu Glu
130 135 140

Ile Asp His Asn Lys Thr Gly Gly Thr Phe Tyr Lys Met Val Arg Asp
145 150 155 160

Asp Lys Thr Ile Tyr Phe Ser Pro Ile Arg Ile Thr Phe Leu Lys Glu
165 170 175

Glu Val Lys Thr Met Tyr Lys Thr Thr Met Gly Ser Asp Gly Phe Ser
180 185 190

Gly Leu Asn His Ile Met Ile Gly His Ser Gln Met Asn Asp Val Cys
195 200 205

Phe Gln Arg Ser Lys Ala Leu Lys Arg Val Gly Leu Asp Pro Ser Leu
210 215 220

Ile Ser Thr Phe Ala Gly Ser Thr Ile Pro Arg Arg Ser Gly Ala Thr
225 230 235 240

Gly Val Ala Ile Lys Gly Gly Thr Leu Val Ala Glu Ala Ile Arg
245 250 255

Phe Ile Gly Arg Ala Met Ala Asp Arg Gly Leu Leu Arg Asp Ile Lys
260 265 270

Printed 03-12-2001

SPECIMEN

6012089

Ala Lys Thr Ala Tyr Glu Lys Ile Leu Leu Asn Leu Lys Asn Lys Cys
275 280 285
Ser Ala Pro Gln Gln Lys Ala Leu Val Asp Gln Val Ile Gly Ser Arg
290 295 300
Asn Pro Gly Ile Ala Asp Ile Glu Asp Leu Thr Leu Leu Ala Arg Ser
305 310 315 320
Met Val Val Val Arg Pro Ser Val Ala Ser Lys Val Val Leu Pro Ile
325 330 335
Ser Ile Tyr Ala Lys Ile Pro Gln Leu Gly Phe Asn Val Glu Glu Tyr
340 345 350
Ser Met Val Gly Tyr Glu Ala Met Ala Leu Tyr Asn Met Ala Thr Pro
355 360 365
Val Ser Ile Leu Arg Met Gly Asp Asp Ala Lys Asp Lys Ser Gln Leu
370 375 380
Phe Phe Met Ser Cys Phe Gly Ala Ala Tyr Glu Asp Leu Arg Val Leu
385 390 395 400
Ser Ala Leu Thr Gly Thr Glu Phe Lys Pro Arg Ser Ala Leu Lys Cys
405 410 415
Lys Gly Phe His Val Pro Ala Lys Glu Gln Val Glu Gly Met Gly Ala
420 425 430
Ala Leu Met Ser Ile Lys Leu Gln Phe Trp Ala Pro Met Thr Arg Ser
435 440 445
Gly Gly Asn Glu Val Gly Gly Asp Gly Gly Ser Gly Gln Ile Ser Cys
450 455 460
Ser Pro Val Phe Ala Val Glu Arg Pro Ile Ala Leu Ser Lys Gln Ala
465 470 475 480
Val Arg Arg Met Leu Ser Met Asn Ile Glu Gly Arg Asp Ala Asp Val
485 490 495
Lys Gly Asn Leu Leu Lys Met Met Asn Asp Ser Met Ala Lys Lys Thr
500 505 510
Ser Gly Asn Ala Phe Ile Gly Lys Lys Met Phe Gln Ile Ser Asp Lys
515 520 525
76

Printed 03/07/2000

SPECIMEN

00120000

Asn Lys Thr Asn Pro Val Glu Ile Pro Ile Lys Gln Thr Ile Pro Asn
530 535 540

Phe Phe Phe Gly Arg Asp Thr Ala Glu Asp Tyr Asp Asp Leu Asp Tyr
545 550 555 560

<210> 32

<211> 100

<212> PRT

<213> Influenza B/Vienna/1/99/na

<400> 32

Met Asn Asn Ala Thr Phe Asn Tyr Thr Asn Val Asn Pro Ile Pro His
1 5 10 15

Ile Arg Gly Ser Val Ile Ile Thr Ile Cys Val Ser Phe Thr Val Ile
20 25 30

Leu Ile Ile Phe Gly Tyr Ile Ala Lys Ile Phe Thr Asn Arg Asn Asn
35 40 45

Cys Thr Asn Asn Ala Ile Gly Leu Cys Lys Arg Ile Lys Cys Ser Gly
50 55 60

Cys Glu Pro Phe Cys Asn Lys Arg Gly Asp Thr Ser Ser Pro Arg Thr
55 70 75 80

Gly Val Asp Ile Pro Ala Phe Ile Leu Pro Gly Leu Asn Leu Ser Glu
85 90 95

Ser Thr Pro Asn
100

<210> 33

<211> 466

<212> PRT

<213> Influenza B/Vienna/1/99/na

<400> 33

Met Leu Pro Ser Thr Ile Gln Thr Leu Thr Leu Phe Leu Thr Ser Gly
1 5 10 15

Printed 06/12/2003

SPECIMEN

0012089

Gly Val Leu Leu Ser Leu Tyr Val Ser Ala Ser Leu Ser Tyr Leu Leu
20 25 30

Tyr Ser Asp Ile Leu Leu Lys Phe Ser Pro Thr Glu Ile Thr Ala Pro
35 40 45

Thr Met Pro Leu Asp Cys Ala Asn Ala Ser Asn Val Gln Ala Val Asn
50 55 60

Arg Ser Ala Thr Lys Gly Val Thr Leu Leu Pro Glu Pro Glu Trp
65 70 75 80

Thr Tyr Pro Arg Leu Ser Cys Pro Gly Ser Thr Phe Gln Lys Ala Leu
85 90 95

Leu Ile Ser Pro His Arg Phe Gly Glu Thr Lys Gly Asn Ser Ala Pro
100 105 110

Leu Ile Ile Arg Glu Pro Phe Ile Ala Cys Gly Pro Lys Glu Cys Lys
115 120 125

His Phe Ala Leu Thr His Tyr Ala Ala Gln Pro Gly Gly Tyr Tyr Asn
130 135 140

Gly Thr Arg Glu Asp Arg Asn Lys Leu Arg His Leu Ile Ser Val Lys
145 150 155 160

Leu Gly Lys Ile Pro Thr Val Glu Asn Ser Ile Phe His Met Ala Ala
165 170 175

Trp Ser Gly Ser Ala Cys His Asp Gly Lys Glu Trp Thr Tyr Ile Gly
180 185 190

Val Asp Gly Pro Asp Ser Asn Ala Leu Leu Lys Ile Lys Tyr Gly Glu
195 200 205

Ala Tyr Thr Asp Thr Tyr His Ser Tyr Ala Asn Asn Ile Leu Arg Thr
210 215 220

Gln Glu Ser Ala Cys Asn Cys Ile Gly Gly Asn Cys Tyr Leu Met Ile
225 230 235 240

Thr Asp Gly Ser Ala Ser Gly Ile Ser Glu Cys Arg Phe Leu Lys Ile
245 250 255

Gln Glu Gly Arg Ile Ile Lys Glu Ile Phe Pro Thr Gly Arg Val Glu
260 265 270

Printed 03-12-2001

SPECIMEN

00120896

His Thr Glu Glu Cys Thr Cys Gly Phe Ala Ser Asn Lys Thr Ile Glu
275 280 285

Cys Ala Cys Arg Asp Asn Ser Tyr Thr Ala Lys Arg Pro Phe Val Lys
290 295 300

Leu Asn Val Glu Thr Asp Thr Ala Glu Ile Arg Leu Met Cys Thr Glu
305 310 315 320

Thr Tyr Leu Asp Thr Pro Arg Pro Asp Asp Gly Ser Ile Thr Gly Pro
325 330 335

Cys Glu Ser Asn Gly Asp Lys Gly Ser Gly Gly Ile Lys Gly Gly Phe
340 345 350

Val His Gln Arg Met Ala Ser Lys Thr Gly Arg Trp Tyr Ser Arg Thr
355 360 365

Met Ser Lys Thr Lys Arg Met Gly Met Gly Leu Tyr Val Lys Tyr Asp
370 375 380

Gly Asp Pro Trp Thr Asp Ser Asp Ala Leu Ala Leu Ser Gly Val Met
385 390 395 400

Val Ser Met Glu Glu Pro Gly Trp Tyr Ser Phe Gly Phe Glu Ile Lys
405 410 415

Asp Lys Lys Cys Asp Val Pro Cys Ile Gly Ile Glu Met Val His Asp
420 425 430

Gly Gly Lys Glu Thr Trp His Ser Ala Ala Thr Ala Ile Tyr Cys Leu
435 440 445

Met Gly Ser Gly Gln Leu Leu Trp Asp Thr Val Thr Gly Val Asn Met
450 455 460

Ala Leu
465

<210> 34.
<211> 248
<212> PRT
<213> Influenza B/Vienna/1/99/ca

<400> 34

Met Ser Leu Phe Gly Asp Thr Ile Ala Tyr Leu Leu Ser Leu Thr Glu
1 5 10 15

Printed 03-12-2001

SPECIMEN

0002889

Asp Gly Glu Gly Lys Ala Glu Leu Ala Glu Lys Leu His Cys Trp Phe
20 25 30

Gly Gly Lys Glu Phe Asp Leu Asp Ser Ala Leu Glu Trp Ile Lys Asn
35 40 45

Lys Arg Cys Leu Thr Asp Ile Gln Lys Ala Leu Ile Gly Ala Ser Ile
50 55 60

Cys Phe Leu Lys Pro Lys Asp Gln Glu Arg Lys Arg Arg Phe Ile Thr
65 70 75 80

Glu Pro Leu Ser Gly Met Gly Thr Thr Ala Thr Lys Lys Lys Gly Leu
85 90 95

Ile Leu Ala Glu Arg Lys Met Arg Arg Cys Val Ser Phe His Glu Ala
100 105 110

Phe Glu Ile Ala Glu Gly His Glu Ser Ser Ala Leu Leu Tyr Cys Leu
115 120 125

Met Val Met Tyr Leu Asn Pro Gly Asn Tyr Ser Met Gln Val Lys Leu
130 135 140

Gly Thr Leu Cys Ala Leu Cys Glu Lys Gln Ala Ser His Ser His Arg
145 150 155 160

Ala His Ser Arg Ala Ala Arg Ser Ser Val Pro Gly Val Arg Arg Glu
165 170 175

Met Gln Met Val Ser Ala Met Asn Thr Ala Lys Thr Met Asn Gly Met
180 185 190

Gly Lys Gly Glu Asp Val Gln Lys Leu Ala Glu Glu Leu Gln Ser Asn
195 200 205

Ile Gly Val Leu Arg Ser Leu Gly Ala Ser Gln Lys Asn Gly Glu Gly
210 215 220

Ile Ala Lys Asp Val Met Glu Val Leu Lys Gln Ser Ser Met Gly Asn
225 230 235 240

Ser Ala Leu Val Lys Lys Tyr Leu
245

<210> 35

Printed 06-12-2000

SPRO

00 26896

<211> 109

<212> PRT

<213> Influenza B/Vienna/1/99/ca

<400> 35

Met Leu Glu Pro Phe Gln Ile Leu Ser Ile Cys Ser Phe Ile Leu Ser
1 5 10 15

Ala Leu His Phe Val Ala Trp Thr Ile Gly His Leu Asn Gln Ile Lys
20 25 30

Arg Gly Val Asn Met Lys Ile Arg Ile Lys Ser Pro Asn Lys Glu Thr
35 40 45

Ile Asn Arg Glu Val Ser Ile Leu Arg His Ser Tyr Gln Lys Glu Ile
50 55 60

Gln Ala Lys Glu Thr Met Lys Glu Val Leu Ser Asp Asn Met Glu Val
65 70 75 80

Leu Gly Asp His Ile Val Ile Glu Gly Leu Ser Ala Glu Glu Ile Ile
85 90 95

Lys Met Gly Glu Thr Val Leu Glu Ile Glu Glu Leu His
100 105

<210> 35

<211> 281

<212> PRT

<213> Influenza B/Vienna/1/99/ca

<400> 36

Met Ala Asn Asn Ile Thr Thr Thr Gln Ile Glu Val Gly Pro Gly Ala
1 5 10 15

Thr Asn Ala Thr Ile Asn Phe Glu Thr Gly Ile Leu Glu Cys Tyr Glu
20 25 30

Arg Leu Ser Trp Gln Arg Ala Leu Asp Tyr Pro Gly Gln Asp Arg Leu
35 40 45

Asn Arg Leu Lys Arg Lys Leu Glu Ser Arg Ile Lys Thr His Asn Lys
50 55 60

Ser Glu Pro Glu Ser Lys Arg Met Ser Leu Glu Glu Arg Lys Ala Ile
65 70 75 80

Printed on 12-2000

SPECIMEN

60-2000

Gly Val Lys Met Met Lys Val Leu Leu Phe Met Asn Pro Ser Ala Gly
85 90 95

Ile Glu Gly Phe Glu Pro Tyr Tyr Met Lys Ser Ser Ser Asn Ser Asn
100 105 110

Cys Pro Lys Tyr Asn Trp Thr Asp Tyr Pro Ser Thr Pro Gly Arg Cys
115 120 125

Leu Asp Asp Ile Glu Glu Pro Glu Asp Val Asp Gly Pro Thr Glu
130 135 140

Ile Val Leu Arg Asp Met Asn Asn Lys Asp Ala Arg Gln Lys Ile Lys
145 150 155 160

Glu Glu Val Asn Thr Gln Lys Glu Gly Lys Phe Arg Leu Thr Ile Lys
165 170 175

Arg Asp Ile Arg Asn Val Leu Ser Leu Arg Val Leu Val Asn Gly Thr
180 185 190

Phe Leu Lys His Pro Asn Gly Tyr Lys Ser Leu Ser Thr Leu His Arg
195 200 205

Leu Asn Ala Tyr Asp Gln Ser Gly Arg Leu Val Ala Lys Leu Val Ala
210 215 220

Thr Asp Asp Leu Thr Val Glu Asp Glu Glu Asp Gly His Arg Ile Leu
225 230 235 240

Asn Ser Leu Phe Glu Arg Leu Asn Glu Gly His Ser Lys Pro Ile Arg
245 250 255

Ala Ala Glu Thr Ala Val Gly Val Leu Ser Gln Phe Gly Gln Glu His
260 265 270

Arg Leu Ser Pro Glu Glu Gly Asp Asn
275 280

<210> 37

<211> 122

<212> PRT

<213> Influenza B/Vienna/1/99/cb

<400> 37

Met Ala Asn Asn Ile Thr Thr Gln Ile Glu Trp Arg Met Lys Lys
1 5 10 15

Printed 09-22-2000

SPEC

COH20896

Met Ala Ile Gly Ser Ser Thr His Ser Ser Ser Val Leu Met Lys Asp
20 25 30

Ile Gln Ser Gln Phe Glu Gln Leu Lys Leu Arg Trp Glu Ser Tyr Pro
35 40 45

Asn Leu Val Lys Ser Thr Asp Tyr His Gln Lys Arg Glu Thr Ile Lys
50 55 60

Leu Val Thr Glu Glu Leu Tyr Leu Leu Ser Lys Arg Ile Asp Asp Asn
65 70 75 80

Ile Leu Phe His Lys Thr Val Ile Ala Asn Ser Ser Ile Ile Ala Asp
85 90 95

Met Val Val Ser Leu Ser Leu Leu Glu Thr Leu Tyr Glu Met Lys Asp
100 105 110

Val Val Glu Val Tyr Ser Arg Gln Cys Leu
115 120